

CLEVELAND
CLINIC
JOURNAL OF
MEDICINE



NAVIGATING THE MANAGEMENT
OF HEPATITIS C

CME ACTIVITY DIRECTOR AND SUPPLEMENT EDITOR:
WILLIAM CAREY, MD
THE CLEVELAND CLINIC

SUPPLEMENT 4 TO VOLUME 70
SEPTEMBER 2003

SPECIAL ISSUE



Supplement 4 to Volume 70, September 2003

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The *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150) is published 12 times yearly by The Cleveland Clinic Foundation.

Subscription rates: U.S. and possessions: personal \$98; institutional \$124; single copy/back issue \$16. Foreign: \$124; single copy/back issue \$16. Institutional (mul-

tiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Postmaster address changes: *Cleveland Clinic Journal of Medicine*, NA32, 9500 Euclid Avenue, Cleveland, OH 44195. Subscription orders, editorial, reprint, and production offices (same address): Phone (216) 444-2661; Fax (216) 444-9385; E-mail ccjm@ccf.org; World Wide Web <http://www.ccjm.org>

Printed in USA.





The epidemiology and natural history of hepatitis C virus infection

NIZAR N. ZEIN, MD

■ ABSTRACT

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States. HCV infection is generally benign in its acute stage but tends to become chronic in more than 70% of patients, at which stage it can induce liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Approximately 2.7 million Americans are estimated to have chronic HCV infection. Although the incidence of HCV infection is believed to be falling, the prevalence of HCV-related liver disease is rising. Better identification of risk factors for HCV transmission and improved understanding of the infection's natural history should refine measures for preventing the spread of infection and preventing complications in those infected.

The story of hepatitis C began a little more than 2 decades ago, when researchers transmitted non-A, non-B hepatitis from patients with transfusion-associated hepatitis to chimpanzees, demonstrating that the disease resulted from a transmissible agent. A major breakthrough came in 1989 with the cloning of the hepatitis C virus (HCV) genome by Choo et al.¹ Shortly after the discovery of HCV, it became apparent that this newly identified virus is the principal causal agent for non-A, non-B hepatitis. The rapid development of sensitive serologic assays for antibodies to HCV led to a large reduction in the incidence of transfusion-associated hepatitis, but it raised many important questions about the epidemi-

ology, natural history, and socioeconomic burden of this viral infection.

In the first years after the discovery of HCV, its primary role in post-transfusion hepatitis and its tendency to induce persistent infection after exposure were widely documented. These early years generated considerable debate about whether HCV was associated with significant morbidity or mortality in infected patients. Compelling evidence, however, linked HCV infection to liver failure and hepatocellular carcinoma (HCC) and was followed by a series of well-designed studies that suggested an increase in liver-related mortality among patients with chronic HCV infection.²⁻⁴ We now firmly recognize that HCV infection is associated with substantial morbidity and mortality and that it clearly represents a global public health challenge.

■ EPIDEMIOLOGY OF HCV INFECTION IN THE UNITED STATES

Worldwide, nearly 170 million people, or about 3% of the global population, are estimated to be infected with HCV.⁵ Although the US infection rate is lower, HCV infection has reached epidemic proportions in the United States and is now the most common chronic blood-borne infection in the nation.⁵

Most people with chronic HCV infection are not aware that they are infected, owing to the symptomless onset of acute HCV infection and the insidious progression of chronic infection. Infected persons serve as a source of transmission to others and are at increased risk for chronic liver disease and other HCV-related chronic systemic disorders. The lack of a prophylactic vaccine or a universally effective therapy has made prevention extremely important in this chronic infection. Identification of infected persons and of risk factors associated with acquiring HCV may allow us to develop strategies to reduce the incidence of HCV infection and control the resulting epidemic.

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Prevalence and incidence of HCV infection

Prevalence. The most accepted figures on the prevalence of HCV infection in the United States are from the Third National Health and Nutrition Examination Survey (NHANES III), a national survey of noninstitutionalized civilians conducted from 1988 through 1994.⁶ Because NHANES III was a population-based household survey, it probably underestimated the prevalence of HCV infection, given the high prevalence of antibodies to HCV in incarcerated, homeless, and institutionalized persons.

Based on findings among 21,000 survey participants tested for antibodies to HCV, the NHANES III researchers estimated that 1.8% of the US population, or approximately 3.9 million Americans, were infected with HCV and that 74% of this group, or approximately 2.7 million Americans, had chronic infection associated with HCV viremia (detectable serum HCV RNA).⁶

NHANES III also delineated racial differences in the prevalence of HCV infection. The prevalence of antibodies to HCV among African Americans (non-Hispanic blacks in NHANES III) was more than twice that among non-Hispanic whites (3.2% vs 1.5%); likewise, the rate of viremia among those with antibodies to HCV was higher in African Americans than in non-Hispanic whites (86% vs 68%). The highest observed prevalence of HCV infection, 9.8%, was among African American men aged 40 to 49 years.⁶

The prevalence of HCV infection is much higher among some specific populations, including patients seen at Veterans Affairs clinics (18% to 40%), prison inmates (40% to 54%), and homeless persons.⁷⁻⁹

Incidence. Estimates of the incidence of HCV infection are more difficult to generate and less likely to be accurate, given the subclinical presentation of acute HCV infection. However, data from the US Centers for Disease Control and Prevention (CDC) suggest that the annual incidence of HCV infection fell from an estimated 230,000 new cases per year in the late 1980s to approximately 35,000 new cases per year in the 1990s.^{5,10} The decline has been attributed mainly to the screening of blood donors for HCV antibodies and to safer needle-use practices among injection-drug users.

Although the incidence of HCV infection may be decreasing, the prevalence of liver disease associated with chronic HCV infection, including liver failure and HCC, is rising.¹⁰ As a result, HCV-related dis-

ease is the leading indication for liver transplantation in the United States.⁵

Methods of HCV transmission

Direct blood or fluid exposure. Direct percutaneous or permucosal exposure to infectious blood or bodily fluid is the most apparent and documented mode of HCV transmission.¹¹ Direct exposure includes transfusion of HCV-contaminated blood products, parenteral drug use, accidental needle injuries in health care workers, and receipt of an organ transplant from an infected donor.

Sexual activity. The risk of acquiring HCV from sexual activity remains controversial.¹² While there is sufficient evidence to support the conclusion that sexual transmission of HCV occurs, the efficiency of this route of transmission appears to be low. The estimated risk of sexual transmission of HCV is 0% to 0.6% per year for those in long-term monogamous relationships, and 1% per year for those with multiple sexual partners.¹² No change in sexual practices is recommended for people in long-term monogamous relationships, whereas those with multiple or short-term sexual partners should use barrier methods of protection against sexually transmitted diseases (STDs).

Higher rates of seropositivity for antibodies to HCV have been reported among prostitutes, homosexual men, and heterosexual men attending STD clinics.¹³⁻¹⁵ Among persons engaged in high-risk sexual behaviors, those with human immunodeficiency virus (HIV) coinfection were more likely to be positive for antibodies to HCV than those who were HIV-negative, even after controlling for factors that may influence sexual transmission.¹⁶ These data suggest that certain sexual behaviors and HIV coinfection are factors that increase the transmission of HCV by sexual contact.

Perinatal transmission. The prevalence of HCV in otherwise healthy children is not known but is much lower than that in adults. Several investigators have reported a relatively high efficiency of vertical mother-to-infant transmission of HCV in mothers coinfecting with HIV.¹⁷ However, mother-to-infant transmission is not efficient (<6% risk of transmission) in mothers who are HIV-negative.¹⁷

Because of their recognized exposure, children born to an HCV-infected woman should be tested for infection. Testing for antibodies to HCV should not be performed before age 15 months to 18 months since these antibodies may be transmitted passively through the placenta in the absence of

Injection-drug use is the transmission route for most cases of HCV infection

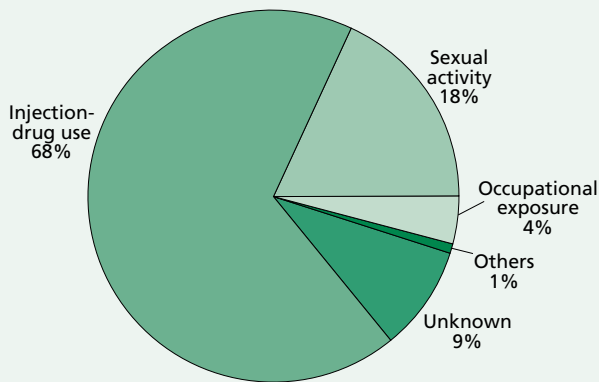


FIGURE 1. Sources of HCV infection in the United States, based on Centers for Disease Control and Prevention data obtained from 1995 to 2000.

HCV infection. Testing for HCV RNA can be done earlier, during the first few weeks of life, to identify infants with active infection, and should be repeated to confirm the results, whether positive or negative. Because HCV is not transmitted through casual contact, there is no reason to exclude HCV-infected children, including those with active infection, from day care or from play at school.¹¹

Occupational exposure. Like sexual and vertical transmission of HCV, occupational transmission has been well documented but is thought to be rare. Prospective studies in health care workers after occupational exposure have documented transmission only after needlestick injuries with contaminated needles. All medical centers should establish policies for counseling health care workers after percutaneous or permucosal exposure (needlestick injuries and blood splashes), testing these workers for HCV, and providing appropriate follow-up care.¹¹

Transmission of HCV from infected health care workers to patients is so rare as to justify publication of individual case reports.¹⁸

Potential risk factors. Several potential risk factors for acquiring HCV, including tattooing, acupuncture, ear piercing, incarceration, military service, and foreign travel, have been evaluated in case-control studies of acute infection and were found not to be associated with HCV transmission.^{6,11} Data from the CDC indicate that injection-drug use accounts for most newly acquired cases of HCV in the United States today, followed by sexu-

al transmission (Figure 1). In only 9% of cases is a source of transmission not identified.

■ NATURAL HISTORY OF HCV INFECTION AND PREDICTORS OF PROGRESSION

Acute infection and chronicity

Acute hepatitis C (detection of HCV RNA in the blood after initial exposure to the virus) is generally a benign disease. In the transfusion setting, where acute onset of HCV infection has been best documented, 70% to 80% of cases are anicteric (not associated with jaundice) and asymptomatic.¹⁹ Acute HCV infection can be severe, but fulminant liver failure associated with acute infection is extremely rare.²⁰ Given the rarity of fulminant disease and the benign nature of acute HCV infection, the significance of HCV infection lies in its tendency to become persistent and induce chronic liver disease.

The rate of chronicity after acute HCV infection is not well established but is believed to exceed 70%.²¹ Several factors that correlate with a lower rate of chronicity have been identified, including younger age at infection, female sex, nonblack race, and development of jaundice during acute infection.²¹ Patients with immunologic deficits are at an increased risk of developing chronic HCV infection.

Complications of chronic infection vary

Several long-term complications may develop in patients with chronic HCV infection, including cirrhosis, end-stage liver disease, and HCC, although there is significant biologic variation among infected patients. This variation became apparent in studies of the natural history of HCV infection. Tong et al²² showed in a retrospective US study that the mean time from HCV exposure at transfusion to the diagnosis of clinical cirrhosis was approximately 21 years, while the mean time to diagnosis of HCC was 28 years. Severe complications such as cirrhosis and HCC developed over a relatively short period (10 to 15 years) in some patients, whereas other patients had no complications despite longer periods of infection. It has been estimated that 20% of patients with chronic HCV infection develop cirrhosis after 20 years of infection.²

These biologic variations in disease outcomes suggest that cofactors might contribute to the outcome of chronic HCV infection. The French team of Poynard et al²³ conducted a multicenter trial that included more than 2,200 HCV-infected patients. Of nine potential cofactors evaluated, three inde-

pendent factors were associated with an increased rate of fibrosis progression:

- Age greater than 40 years at the time of HCV infection
- Daily consumption of more than 50 g of alcohol
- Male sex.

Among factors not associated with more advanced liver disease were HCV genotype and serum HCV RNA level.²³

Other cofactors have been associated with more severe HCV-related liver disease in other studies, including race (black patients are less likely to progress to cirrhosis), coinfection with other viruses, such as hepatitis B virus and HIV, and genetic influences.^{24–26}

Hepatocellular carcinoma

The development of HCC in HCV-infected patients is particularly significant, given the number of patients with chronic HCV infection and the poor outcome of HCC. The risk of HCC is estimated to be up to 17 times greater in HCV-infected patients than in their HCV-negative counterparts.²⁷ Underlying cirrhosis appears to be a prerequisite for the development of HCC in patients with chronic HCV infection. Among patients in whom cirrhosis is established, the estimated annual incidence of HCC is 1% to 4%.^{28,29}

In light of these findings, routine screening for HCC is currently recommended for patients with HCV infection; patients should be screened at 6-month intervals using serum alpha fetoprotein level and hepatic ultrasound examination.³⁰ Antiviral therapy with interferon may reduce the risk of HCC in patients with chronic HCV infection, although this remains an issue of debate.²⁷

Extrahepatic manifestations

Another dilemma in the natural history of chronic HCV infection is the development of extrahepatic manifestations. **Table 1** lists some of the most common of these.^{31–37} It remains to be shown whether these conditions are directly caused by HCV infection or result from underlying liver disease.

HCV-related cryoglobulinemia is the most frequent extrahepatic manifestation of HCV and has been reported in up to 50% of patients. Symptomatic cryoglobulinemia is uncommon, however, occurring in less than 1% of patients. Symptomatic cryoglobulinemia presents clinically with manifestations of vasculitis, including skin rash, renal dysfunction, neuropathy, and fatigue. Cryoglobulin-

TABLE 1
Extrahepatic manifestations
of chronic HCV infection

Essential mixed cryoglobulinemia
Porphyria cutanea tarda
Membranoproliferative glomerulonephritis
Diabetes mellitus
Autoimmune thyroiditis
Sjögren syndrome
Lichen planus
Lymphoma

emia typically responds to interferon therapy for HCV infection, but relapse is common once therapy is stopped in those who do not achieve sustained viral eradication.

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Tests and screening strategies for the diagnosis of hepatitis C

WILLIAM CAREY, MD

■ ABSTRACT

The threshold for testing for hepatitis C virus (HCV) should be low for persons with any risk factor for HCV infection. Current practice calls for first screening for antibodies to HCV and then testing for HCV RNA in those in whom antibodies are detected. Viral testing can distinguish between active and resolved HCV infection and also determine viral load, which can help predict response to antiviral therapy. Many highly sensitive assays are available for testing for HCV RNA. Once HCV infection is diagnosed, the HCV genotype should be determined to help predict treatment response and duration. Liver biopsy can aid in disease staging and help guide treatment decisions. Practical and efficient screening strategies for HCV are guided by risk factors for HCV infection.

Physicians need to understand effective strategies for establishing or excluding a diagnosis of hepatitis C, given the prevalence of hepatitis C virus (HCV) infection and its potentially serious complications. This article reviews current information to guide strategies for diagnosing or excluding hepatitis C and to support the correct interpretation of screening tests.

■ HEPATITIS C: COMMON, POTENTIALLY SERIOUS

Infection with HCV is the most common chronic blood-borne viral infection in North America. An estimated 3.9 million people in the United States have been exposed to HCV, and 2.7 million have

measurable HCV RNA. An estimated 38,000 are newly infected annually. More than 5% of certain demographic groups are infected.¹

Although the natural history of HCV infection is often benign, over time 20% of infected individuals develop serious sequelae, such as severe fibrosis, cirrhosis, end-stage liver disease, or hepatoma. Some develop extrahepatic manifestations, such as lichen planus, leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, porphyria cutanea tarda, or B-cell lymphoma.

■ WHY TEST FOR HCV?

Testing and testing sequences for HCV infection depend upon the clinical question to be answered, which usually is one of the following:

- Does this patient have hepatitis C?
- Has this person (eg, a potential blood donor) ever been exposed to HCV?
- What effect has HCV infection had on the liver?
- What is the likelihood that treatment will be effective in this patient?
- Has treatment been effective?

■ CANDIDATES FOR HCV TESTING

Broadly speaking, there are four categories of candidates for HCV testing:

- Those who have risk factors for HCV infection
- Those with abnormal liver function test results
- Blood donors
- HCV-infected patients undergoing antiviral therapy.

Testing needs differ for each category. Testing the general population for HCV is not cost-effective. However, the threshold for testing should be low for persons with any risk factor. A history of relevant HCV exposure is important.

The principal mode of transmission is parenteral exposure to infected blood or blood products. Those

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with a history of illicit injection-drug use are at highest risk. Blood transfusions prior to 1992 carry a 5% to 7% risk of HCV infection for each unit of blood transfused. Exposure to blood from unclean needles used in tattooing or body piercing also risks HCV infection. Sexual contact with an infected person poses only a small risk.

Certain groups are at unusually high risk, such as prison inmates and people with low socioeconomic status. Many infected individuals deny all recognized risk factors. This suggests either forgetfulness or the possible presence of other, as-yet-unrecognized modes of transmission.

■ LAB TESTING: OPTIONS AND STRATEGIES

Laboratory testing forms the basis for establishing or rejecting the diagnosis of hepatitis C. Liver biopsy is needed in most patients if accurate staging is desired.

Laboratory tests have evolved in diversity, sensitivity, and specificity. Historically, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were used, even though they are nothing more than surrogate markers for HCV. Aminotransferase testing has been replaced by tests that measure either antibody to HCV (anti-HCV) or viral presence. The current practice of first screening for anti-HCV and then testing for the virus in those in whom antibodies are detected represents a compromise between cost and efficiency: antibody testing is inexpensive, while viral testing is costly. When viral testing becomes less expensive, it will be reasonable to use viral testing as the first screening test and primary diagnostic tool in most clinical situations.

Aminotransferase levels: No longer useful

Levels of aminotransferases (ALT, AST) in the blood indicate the degree to which liver membrane injury has resulted in an increased release of hepatocellular enzyme into the bloodstream. Because ALT is more specific than AST for liver injury, ALT is used more often. In patients with risk factors for HCV infection (see above) and in whom there is no other explanation for increased enzyme levels, elevated aminotransferase levels are highly associated with HCV infection. Indeed, an elevated ALT level remains a reason to reject a potential blood donor.

Early studies of interferon alfa, which formed the basis for its original approval by the US Food and Drug Administration for treatment of hepatitis C, were done before the advent of testing for anti-HCV or viral RNA. In these studies, the presence of

risk factors plus an elevated ALT level was taken as evidence that HCV was present.

At the same time, an elevated ALT level may be seen in a number of other disorders, limiting its specificity. Moreover, HCV infection may not elicit an ALT elevation.² As many as 30% of HCV-infected people have persistently normal ALT values. Some with normal ALT values may have advanced liver disease; ALT levels tend to fall as cirrhosis develops.³ It remains true, however, that when the ALT level, all other standard liver function measures (AST, alkaline phosphatase, bilirubin, immunoglobulins, albumin), and the complete blood cell count are normal in an HCV-infected person, the likelihood of significant liver disease is very low.⁴ This is especially true if the patient has no liver comorbidities, such as significant alcohol consumption, and is not obese.

Modeling studies have assessed the use of ALT values as the first screen for HCV, followed by more specific viral tests for those with elevated ALT levels.⁵ As discussed in detail later, this was the most expensive of several strategies tested.

In summary, ALT and other markers of liver injury are no longer appropriate for selecting who should be tested for hepatitis C.

Antibody tests: A helpful first screen

A number of tests are available for detecting the presence of anti-HCV. The most commonly used are the enzyme immunoassay (EIA) and the enzyme-linked immunosorbent assay (ELISA), which is a type of EIA. These tests cost less than \$50 and are rapid, easy to perform, and widely available. Early versions were plagued by frequent false-positive reactions, but the current “third-generation” assays are 99% specific and 99% sensitive in immunocompetent individuals.⁶

To confer specificity on a positive EIA result, a test has been introduced that contains four antigens from HCV, embedded on a strip, and uses a recombinant immunoblot assay (RIBA) technique. The presence of antibodies to two or more of the antigens embedded on the test strip represents a positive result. Detection of only one antibody represents an indeterminate result. Very rarely, antibodies to superoxide dismutase are present, so the test strip contains a fifth region to test for these antibodies. In such cases, the RIBA result is uninterpretable. A positive RIBA result is almost always a true positive—ie, a marker of current or past infection.

Many clinical laboratories automatically test for

anti-HCV by RIBA when an EIA result is positive, to confirm that the result is a true positive. Given the remarkable improvement in third-generation EIAs, RIBA testing is no longer necessary as a routine add-on to confirm all positive EIA results. A positive EIA should instead be followed by viral testing for HCV. RIBA testing remains useful when a patient tests positive for anti-HCV by EIA but has no viremia. In such a case, a negative RIBA result probably indicates a false-positive EIA antibody test, whereas a positive RIBA suggests resolved HCV infection.

Rarely, an HCV-infected person will not express antibody to HCV. This lack of antibody expression is described mostly in immunosuppressed patients, and most often in those on chronic hemodialysis. It is clear that HCV can persist in and be transmitted by these individuals even if they remain negative for anti-HCV by both EIA and RIBA. This possibility should be considered when screening for HCV in selected populations (eg, patients undergoing transplantation and patients on chronic dialysis).⁷

Viral testing: A watershed in HCV evaluation

The presence of antibodies to HCV cannot distinguish between current and resolved infection. Moreover, it does not have any bearing on the likelihood of successful antiviral treatment. The advent of serum-based tests of viral presence represents a watershed in the evaluation and management of hepatitis C.

Several assays are in use for the detection of HCV RNA, and infected patients may be tested in several laboratories, each using a different test procedure. Until recently, even the units of expression lacked standardization. Many studies of HCV therapy expressed the amount of virus present (viral load) in copies per mL. Several studies selected 2 million copies per mL as the threshold separating “low” from “high” viral load. However, because there was no comparability of quantified viral loads between assays, it was virtually impossible to interpret viral loads when different test systems were used.

Assays now are standardized and expressed in IU per mL of serum.⁸ A viral load greater than 800,000 IU/mL is currently considered high, regardless of the assay used. **Table 1** lists the assays in common use in the United States and their lower limits of detection.

Target vs signal amplification. The test most commonly used to determine the presence or absence of HCV is based on the polymerase chain reaction

TABLE 1
Commonly used tests for detecting HCV RNA

Assay type and brands	Manufacturer	Detection limit* (IU/mL)
QUALITATIVE TESTS		
Polymerase chain reaction		
Amplicor HCV v2.0	Roche Molecular Systems	50
Transcription-mediated amplification		
Versant HCV RNA Qualitative Assay	Bayer Diagnostics	10
QUANTITATIVE TESTS		
Polymerase chain reaction		
LCx HCV RNA Quantitative Assay	Abbott Diagnostics	25
SuperQuant	National Genetics Institute	30
Amplicor HCV Monitor v2.0	Roche Molecular Systems	600
Cobas Amplicor HCV Monitor	Roche Molecular Systems	600
Branched DNA		
Versant HCV RNA 3.0 Quantitative Assay	Bayer Diagnostics	615

*Most untreated patients with HCV infection have 50,000 to 5,000,000 IU/mL, so differences in the lower limit of detection are usually not important. See text.

(PCR). This test detects the presence of minute quantities of HCV by first amplifying the quantity of HCV RNA in the sample, a technique referred to as *target amplification*. Transcription-mediated amplification is another target amplification test.

Other tests, such as the branched DNA assay, operate by a different mechanism, referred to as *signal amplification*. The first step in branched DNA testing is to bind a signal to the virus, after which the signal is amplified.

Most target amplification tests such as PCR are more sensitive than currently available signal amplification tests, and so yield fewer false-negative results. Target amplification tests are more complicated and more costly than signal amplification tests, and also take longer to perform. Signal amplification tests are technically simple, highly automated, rapid, and easily reproduced. Their relative lack of sensitivity is their main drawback. Both types of tests are extremely specific. Apart from a

TABLE 2
Guide to the interpretation of hepatitis C testing

Antibody to HCV	HCV RNA	Usual interpretation	Other possible interpretation
Negative	Negative	No infection	—
Positive	Positive	HCV present	—
Positive	Negative	Resolved infection	1. False-positive (<1%) 2. Treated, HCV below detectable limits (verify with qualitative HCV RNA PCR)
Negative	Positive	Infection present (usually in immunocompromised patients or patients undergoing hemodialysis)	1. Early infection 2. False-positive or contaminated test system

contaminated system, false-positive results are rare.

The current generation of PCR tests are quite sensitive, detecting HCV viral loads as low as 25 IU/mL. Levels of circulating HCV in individuals with untreated infection usually range from 50,000 to 5,000,00 IU/mL.

Qualitative vs quantitative assays. The HCV RNA test kits designed to indicate viral load are not quite as sensitive as those that provide only a qualitative (present/absent) result. Because untreated individuals with HCV have viral levels so much higher than the threshold of detection, this small loss in sensitivity is not important, and quantitative HCV RNA testing should be ordered for these patients. **Table 1** illustrates the narrow gap between the most sensitive qualitative and quantitative tests.

Results of qualitative PCR tests for HCV RNA are expressed as either positive or negative; viral load is not provided. Because of the slight loss in sensitivity with quantitative assays, a negative result on a quantitative PCR or branched DNA assay may be falsely negative and, in a person with suspected HCV infection, should be confirmed with a qualitative PCR test for HCV RNA. This is especially true when assessing treatment response.

Why is viral load important? There is no correlation between viral load and histologic disease activity, but patients with high viral load have a lesser likelihood of responding to available antiviral therapy.⁹

In addition, viral load has implications for therapeutic “stopping rules.” It is now clear that patients with HCV genotype 1 who do not achieve a 100-fold reduction in viral load after 12 weeks of antiviral therapy have less than a 5% chance of achieving

such a response if therapy is continued for an entire year. As a result, antiviral therapy generally should be stopped after 12 weeks in such patients, since continuing treatment is usually not worth the associated cost and morbidity, given the low response rate. However, this criterion of a 100-fold reduction in viral load at 12 weeks does not apply to patients with HCV genotype 2 or 3, since such patients require only 6 months of antiviral therapy.¹⁰

■ HCV GENOTYPES

The genomic heterogeneity of HCV has impeded the development of effective vaccines. Every strain of HCV demonstrates genomic variability over time. Such changes are referred to as quasispeciation.

More fundamental and more stable genomic differences in HCV allow classification of HCV into genotypes. Until recently, six major genotypes were recognized. Some HCV isolates in Vietnam fall outside these major genotypes, and three additional genotypes are now recognized, bringing the number of principal genotypes to nine. Several genotypes are subclassified as a or b (eg, genotype 1a or 1b), but these distinctions are of little clinical usefulness. Line probe assays used to determine genotype may misclassify patients of Southeast Asian ancestry who have genotype 7, 8, or 9 as having genotype 1b.

The frequency of the different HCV genotypes varies significantly with geography. Genotypes 1, 2, and 3 account for the vast majority of cases of HCV infection in North America; among these, genotype 1 predominates, accounting for 70% to 75% of North American cases. Genotype 4 is most common in Egypt and the Arabian peninsula.

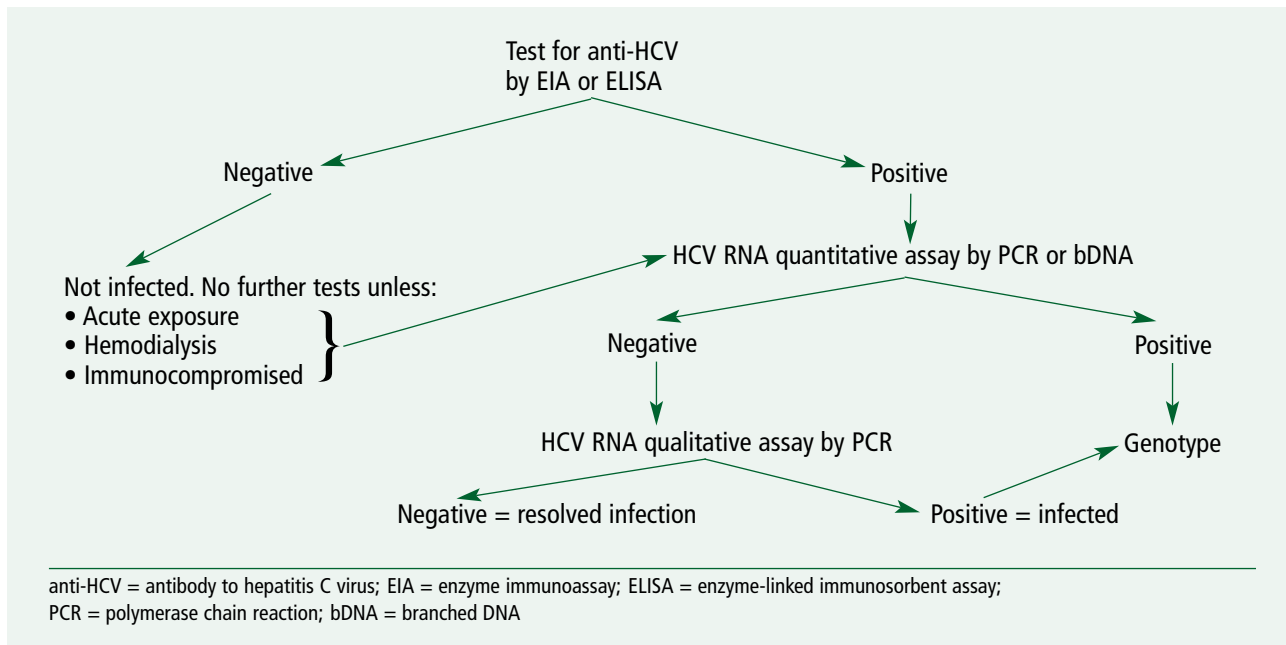


FIGURE 1. Algorithm for laboratory investigation of suspected HCV infection.

Genotype predicts treatment response, duration

Genotype does not have an important bearing on the virulence of HCV but instead relates most closely to anticipated treatment response and treatment duration.

HCV genotypes 2 and 3 are most likely to respond to antiviral therapy. Combination therapy with peginterferon alfa and ribavirin achieves a sustained virologic response in about 80% of previously untreated and noncirrhotic patients with HCV genotype 2 or 3, compared with about 50% of those with genotype 1. Moreover, patients with HCV genotype 2 or 3 require treatment for only 6 months to achieve maximal therapeutic benefit, whereas patients with genotype 1 require 12 months of therapy for maximal benefit. For these reasons, it is customary and appropriate to determine the HCV genotype in all infected patients who are being considered for antiviral therapy. Southeast Asian patients with genotype 7, 8, or 9 have a better response to antiviral therapy than do those with genotype 1.¹¹

■ LIVER BIOPSY

The histologic features of chronic hepatitis C are well defined. Two components are considered: the degree of inflammation and hepatocyte necrosis (activity), and the hepatic response (fibrosis).

Activity is gauged by how many mononuclear inflammatory cells are present in and around the portal areas, and by the number of dead or dying hepatocytes. Activity changes do not imply progressive disease.

Fibrosis, more than inflammation, predicts progression to irreversible liver disease in patients with hepatitis C. HCV elicits a variable fibrotic response. Mild fibrotic reactions in the portal and periportal regions are the earliest changes that imply possible progression to cirrhosis. Intermediate fibrotic changes are present when the fibrosis extends from one portal area to another. This is termed “bridging fibrosis.” In some, this reaction may evolve into frank cirrhosis. Other histologic changes, such as a mild or moderate amount of macrovesicular fat (steatosis), may also be seen in HCV-infected patients.

Standardized evaluation of liver histology in HCV infection is helpful, and several histologic grading scales have been developed and validated. Each considers the degree of liver pathology in terms of the amount of inflammation and the amount of fibrosis. **Table 3** profiles three common histology grading scales.^{12–14} Among the three, the METAVIR system¹⁴ is particularly simple and easy to learn. It has been extensively validated.¹⁵

TABLE 3
Histologic grading and staging in hepatitis C

Scale	Necro-inflammation	Fibrosis	Total score
Histology Activity Index (HAI) ¹²	0–18	0–4	0–22
Ishak modified HAI ¹³	0–18	0–6	0–24
METAVIR ¹⁴	0–3	0–4	0–7

What's the role of liver biopsy in the evaluation of hepatitis C?

Liver biopsy is not necessary to establish the diagnosis of hepatitis C. All of the histologic findings seen in hepatitis C, individually and collectively, may be seen in other viral and nonviral liver diseases, so none is diagnostic of HCV infection. Serum-based tests are precise and unequivocal: an individual positive for HCV RNA is infected.

It is true, however, that histologic changes that are markedly different from those seen in hepatitis C (eg, Mallory hyaline, polymorphonuclear inflammation, granulomas, heavy pigment deposition from iron overload) may suggest a diagnosis in addition to hepatitis C. Still, absent other clinical or laboratory findings suggesting a second liver pathology, a liver biopsy will seldom alter the diagnosis. We have shown that liver biopsy in those with HCV infection diagnosed by serum-based tests never eliminates the diagnosis of HCV.¹⁶ Moreover, additional liver diagnoses were made in only 2% of patients.¹⁶

Liver biopsy figures into the evaluation of hepatitis C by aiding with disease staging (ie, defining the amount of fibrosis and the presence or absence of cirrhosis) in ways that cannot be done without invasive testing. In a patient series at our institution, cirrhosis was found in 29% of cases of hepatitis C that came to biopsy.¹⁶ Using a published cirrhotic discriminant score for clinical diagnosis of cirrhosis in these cases would have confidently established or excluded a diagnosis of cirrhosis in only 23% of these cirrhosis cases. In the remainder, liver biopsy was critical for proper staging. These findings have recently been confirmed.¹⁷ Others have found that laboratory tests (eg, AST:ALT ratio; platelet counts; measures of hyaluronic acid, fibronectin, pseudocholinesterase, etc) are not suffi-

ciently sensitive in predicting the histologic changes of severe fibrosis or cirrhosis.¹⁸

In many cases, knowledge of the presence (or absence) of cirrhosis is clinically relevant. All other features held constant, the presence of bridging fibrosis or cirrhosis reduces the expected response rate to antiviral therapy. Major shifts in expected outcome are far from trivial and often alter the clinical decision to treat.¹⁹ Moreover, pretreatment liver biopsy can determine whether cirrhosis prevention is a reasonable treatment goal. Finding cirrhosis on biopsy also can influence management by prompting entry into surveillance programs for hepatoma and esophageal varices.

Liver biopsy remains an important tool in the thorough baseline evaluation of the HCV-infected patient. How frequently, or even if, sequential biopsies should be performed in the HCV-infected patient has not been established. There seems to be little need for routine biopsies after a course of antiviral therapy. In clinical practice, authorities differ with respect to rebiopsy at intervals to restage the liver in HCV infection. I do not recommend routine follow-up biopsies.

■ SCREENING STRATEGIES: HCV RISK FACTORS SHOULD BE THE GUIDE

The tests described above give rise to many possible screening strategies to find cases of HCV infection at an early stage. The costs and yield of several possible screening strategies were explored in an analysis constructed from a large database derived from the National Hepatitis Surveillance Program, conducted in 1992.⁵ One strategy called for testing for HCV only in those individuals who had a greater than 7% likelihood of infection based on an empirically derived mathematical model. Other strategies tested for HCV only if significant risk factors were uncovered in a simple questionnaire. A final strategy tested for HCV only if the ALT level was elevated.

The analysis found that use of the predictive mathematical model was the most effective and efficient means of deciding who should have HCV testing.⁵ Unfortunately, such a model is too arcane and unwieldy to be clinically applicable. However, one of the risk-based screening strategies was associated with very similar costs per 100 persons screened, costs per case detected, and marginal costs per case detected. Specifically, this strategy tested for HCV in those who reported risk factors:

- History of intravenous drug use
- Sex with an intravenous drug user
- Blood transfusion before 1992
- Hemodialysis
- Employment in health care.

(This list of risk factors should be expanded to include other modes of blood–blood transmission, including tattoos and body piercings, intranasal cocaine use, and having an HCV-infected mother.)

The least efficient strategy was to screen by measuring ALT and then testing for HCV in cases of an elevated ALT level. The lesson of this analysis is that testing for HCV infection should be offered to those with risk factors for infection, regardless of ALT level.

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Management of newly diagnosed hepatitis C virus infection

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■ ABSTRACT

All patients with chronic hepatitis C virus infection are potential candidates for antiviral therapy. Careful patient selection can optimize the response to therapy and enhance safety. Pegylated forms of interferon, when combined with ribavirin, can "cure" the majority of patients undergoing therapy, and these agents have become the new standard of care for chronic hepatitis C. Careful and timely management of side effects, which are experienced by all patients, can improve adherence to antiviral therapy and further improve response rates.

The majority of patients infected with hepatitis C virus (HCV) can now be cured with a combination of the new pegylated forms of interferon plus ribavirin. These new regimens represent an important advance in the treatment of hepatitis C, but their safe and effective use in individual patients requires many careful clinical decisions. This article reviews these newest regimens for treating HCV infection, discusses how to determine a patient's eligibility for antiviral therapy for hepatitis C, and explores how to manage the adverse events commonly encountered during treatment.

■ WHO IS ELIGIBLE FOR HCV THERAPY?

Once the diagnosis of chronic HCV infection is established, the clinician must be ready to discuss treatment options with the patient and establish a plan for long-term management.

The recent National Institutes of Health consensus statement on hepatitis C noted that all patients with chronic hepatitis C are potential candidates for thera-

py.¹ In practice, however, many patients with chronic hepatitis C have significant comorbidities or other conditions that are contraindications to combination antiviral regimens for HCV infection, be they pegylated interferon alfa (peginterferon) plus ribavirin or standard interferon alfa plus ribavirin.^{2,3} These exclusions to treatment are based on the well-established side effect profiles of these agents (discussed below), which may result in serious adverse events in high-risk patient groups.⁴ Therefore, before initiating antiviral therapy for HCV infection, physicians must thoroughly examine the risks and benefits of therapy in the context of the individual patient's medical history.

Absolute contraindications

Combination therapy with interferon (including peginterferons) plus ribavirin should never be initiated in the following patients:

- Female patients who (and male patients whose female partners) are pregnant, contemplating pregnancy, or unwilling to use adequate contraception (because of ribavirin's teratogenic effects)
- Patients with poorly controlled psychiatric disease, including recent history of suicide attempt (because of the psychiatric effects of interferons)
- Patients with symptomatic coronary artery disease (because of ribavirin-induced anemia).

Potential contraindications, other cautions

Numerous other contraindications to therapy and cautions are noted in the package inserts of these antiviral agents. Among them:

- Autoimmune hepatitis or other well-documented autoimmune disease (because of exacerbation of immune-mediated diseases by interferons)
- Hepatic decompensation (Child-Pugh class B or C)
- Hemoglobinopathies (because of hemolysis from ribavirin)
- Breast-feeding
- Bipolar illness
- Renal insufficiency with creatinine clearance less

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than 50 mL/min (due to ribavirin's renal clearance)

- Preexisting neutropenia ($< 1,500$ cells/mm³), a platelet count less than 90,000 cells/mm³, or hemoglobin less than 10 g/dL.

Some of these cautions may be considered relative, rather than absolute, contraindications to therapy, requiring treatment decisions to be individualized. An example would be a patient with well-compensated cirrhosis with hypersplenism. Although such a patient may not meet strict eligibility criteria because of cytopenias, this type of patient arguably has the most to gain from viral eradication, and a case can be made for the safe execution of treatment under careful monitoring. Similarly, the presence of an isolated antinuclear antibody or other autoantibody should not be considered a contraindication to therapy unless other clinical features of autoimmune hepatitis or systemic autoimmune diseases are apparent.⁵

■ HCV ERADICATION IS THE TREATMENT GOAL

The goal of therapy for hepatitis C is permanent eradication of HCV RNA from the serum. Sustained virologic response (SVR), defined as undetectability of HCV RNA in the serum by a sensitive nucleic acid assay 6 months after the completion of antiviral therapy, is synonymous with "cure" of HCV infection. It is well established that relapse beyond this 6-month post-treatment time point is unusual.⁶ Furthermore, HCV RNA cannot be detected in liver tissue from patients who achieved SVR to antiviral therapy.⁷

Both of the new peginterferons (peginterferon alfa-2a [Pegasys] and peginterferon alfa-2b [PEG-Intron]) have demonstrated superiority in achieving SVR as monotherapy compared with standard interferon alfa,⁸⁻¹⁰ and combination therapy with peginterferon and ribavirin has been established as the best available treatment for patients with chronic hepatitis C.¹

■ PHARMACOKINETICS OF PEGINTERFERON

The peginterferons were developed by adding a polyethylene glycol (PEG) moiety to an interferon molecule, which alters the pharmacokinetic properties of the native protein, resulting in a prolonged serum half-life and the ability to administer the compound once weekly rather than three times weekly.

Peginterferon alfa-2a encompasses a branched, 40-kilodalton PEG moiety, whereas peginterferon alfa-2b encompasses a linear 12-kilodalton PEG moiety. Differences in the pharmacokinetic properties of peginterferons, such as serum half-life, are dependent on the size and configuration of the attached PEG

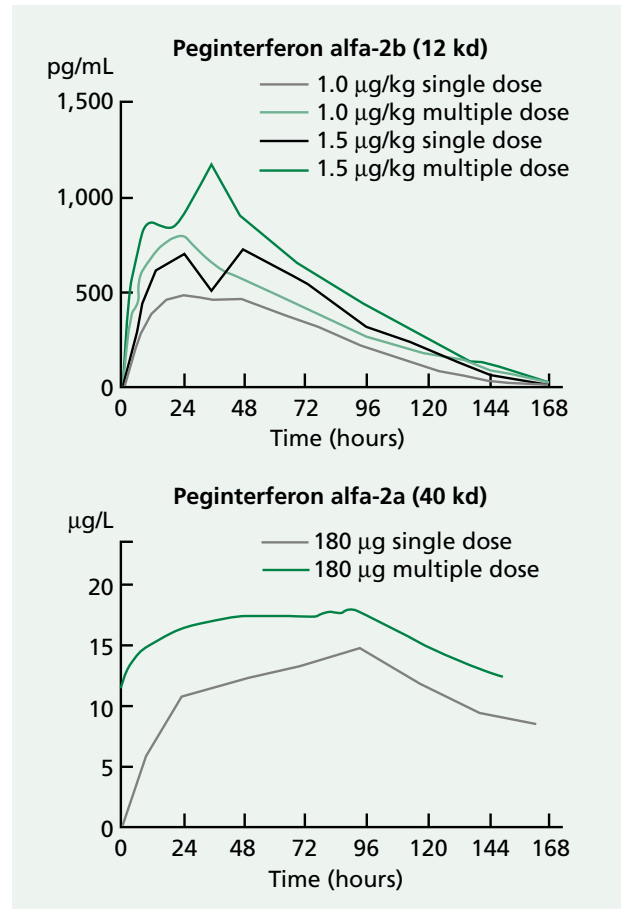


FIGURE 1. Mean serum concentration–time profiles of the peginterferons after administration of single and multiple doses (based on data from refs. 27 and 28). These agents' prolonged serum half-life allows once-weekly dosing.

moiety (Figure 1). In addition, the large PEG moiety of peginterferon alfa-2a strictly limits its volume of distribution so that a standard 180-µg dose is suitable for all patients. In contrast, peginterferon alfa-2b has a large volume of distribution, requiring that its dose be adjusted according to patient weight (1.5 µg/kg/week is recommended when used in combination with ribavirin). Like standard interferon, both peginterferons are given by subcutaneous injection.

■ CLINICAL TRIALS OF THE PEGINTERFERONS

Peginterferon alfa-2b and ribavirin

Manns et al¹¹ reported results from the first randomized trial of peginterferon alfa-2b combined with ribavirin. In this study, 1,530 patients with chronic hepatitis C were randomized to one of three combination regimens:

- Peginterferon alfa-2b 1.5 µg/kg/week plus riba-

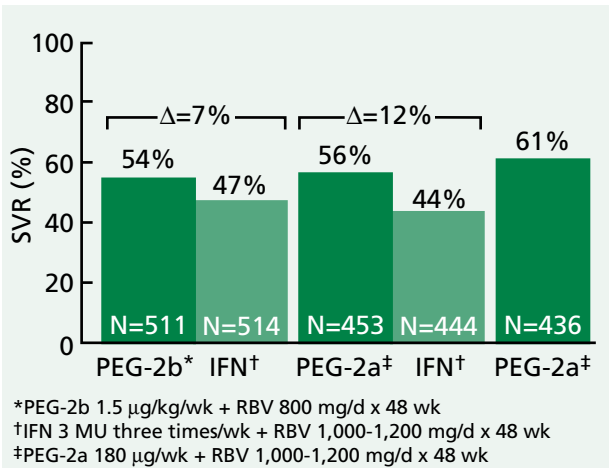


FIGURE 2. Sustained virologic response (SVR) rates from phase 3 studies of peginterferon alfa-2b (PEG-2b) and peginterferon alfa-2a (PEG-2a) compared with interferon alfa-2b (IFN). All regimens also included ribavirin (RBV). Results are by intention-to-treat analysis. Data for the two leftmost bars are from ref. 11, data for the two middle bars are from ref. 13, and data for the rightmost bar are from ref. 16, which had no IFN control arm.

virin 800 mg/day, both for 48 weeks

- Peginterferon alfa-2b 0.5 µg/kg/week for 44 weeks (after an initial 4 weeks of 1.5 µg/kg/week) plus ribavirin 1,000 to 1,200 mg/day for 48 weeks
- Interferon alfa-2b 3 MU three times weekly plus ribavirin 1,000 to 1,200 mg/day, both for 48 weeks.

At 24 weeks after the end of treatment, SVR was achieved in 54% of patients in the higher-dose peginterferon group compared with 47% of patients in each of the other treatment arms ($P = .01$) (Figure 2).¹¹

Among patients with HCV genotype 1 (a difficult-to-treat group; see below), SVR was achieved in 42% of those treated with the higher dose of peginterferon compared with 33% of those treated with standard interferon.¹¹ Among patients with the most treatment-resistant characteristics, genotype 1 and high levels of HCV viremia (> 2 million copies/mL), SVR was achieved in 30% of higher-dose peginterferon recipients and 29% of standard interferon recipients.¹² In contrast, patients with more favorable virologic characteristics (ie, HCV genotype 2 or 3) achieved SVR rates of approximately 80% across all treatment groups.

Peginterferon alfa-2a and ribavirin

Fried and colleagues¹³ reported results from the first phase 3 trial to evaluate the combination of peginterferon alfa-2a and ribavirin in previously untreated patients with chronic hepatitis C. Patients were treated for 48 weeks and followed for an additional

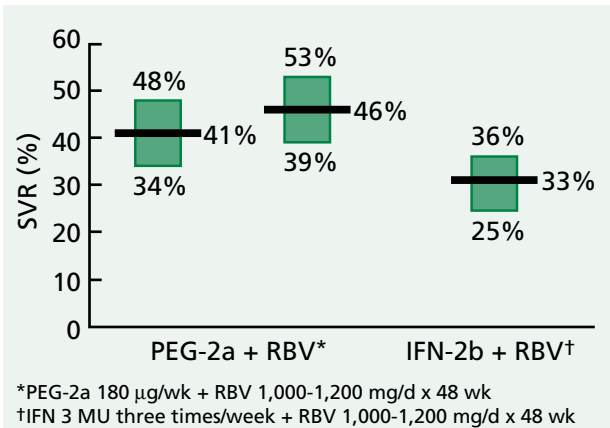


FIGURE 3. Sustained virologic response (SVR) rates in treatment-resistant patients (ie, with HCV genotype 1 and high levels of HCV RNA > 2 million copies/mL) in phase 3 studies of peginterferon alfa-2a plus ribavirin (RBV). Green bars represent 95% confidence intervals. The peginterferon data are from ref. 13 (left bar) and ref. 16 (middle bar). The right bar presents control SVR data for interferon alfa-2b plus ribavirin from ref. 13.

24 weeks to determine SVR rates. A total of 1,121 patients were randomly assigned to one of the following regimens:

- Peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day
- Peginterferon alfa-2a 180 µg/week plus placebo
- Interferon alfa-2b 3 MU three times weekly plus ribavirin 1,000 to 1,200 mg/day.

The SVR rate was significantly higher in patients treated with peginterferon and ribavirin (56%) than in those receiving standard interferon and ribavirin (44%, $P < .001$) or peginterferon and placebo (29%, $P < .001$) (Figure 2). Among patients with HCV genotype 1, SVR was attained in 46% of those receiving peginterferon and ribavirin compared with 36% of those receiving standard interferon and ribavirin ($P = .01$) Among patients with both genotype 1 and high levels of HCV viremia (> 2 million copies/mL), SVR was achieved in 41% of peginterferon/ribavirin recipients compared with 33% of standard interferon/ribavirin recipients (Figure 3).¹³

■ GENOTYPE AND OTHER FACTORS AFFECT TREATMENT DURATION AND RIBAVIRIN DOSE

HCV genotype is the single factor that is most strongly predictive of treatment response to all approved antiviral agents.^{11,13-16} Patients with genotype 1 have lower response rates than patients with genotypes 2 or 3. Given the variability in SVR rates to similar treatment regimens, it is conceivable that

Treatment duration and ribavirin dose matter in patients with HCV genotype 1

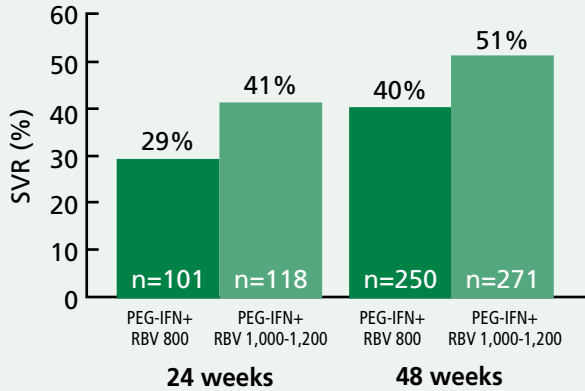


FIGURE 4. Rates of sustained virologic response (SVR) among patients with HCV genotype 1 in a phase 3 study of peginterferon alfa-2a (PEG-IFN) plus ribavirin (RBV).¹⁶ Patients were treated for 24 or 48 weeks and received either a low (800 mg/day) or high (1,000–1,200 mg/day) dose of ribavirin. Higher SVR rates were associated with longer treatment and higher ribavirin dose.

a patient’s antiviral regimen could be tailored to his or her specific characteristics to increase the likelihood of response and minimize the costs and side effects of therapy.

The first prospective study to evaluate this possibility was a phase 3 trial¹⁶ designed to assess the impact of treatment duration and ribavirin dose in patients receiving peginterferon alfa-2a and ribavirin. Patients were randomized to 24 or 48 weeks of treatment with peginterferon alfa-2a 180 µg/week and ribavirin at either 800 mg/day or 1,000 to 1,200 mg/day.

The overall SVR rate was 61% for patients treated for 48 weeks with peginterferon and the higher dose of ribavirin. Patients with HCV genotype 1 who received this regimen had an SVR rate of 51%. In contrast, patients with genotype 1 who received treatment for only 24 weeks (both the high-dose and low-dose ribavirin groups) had lower SVR rates (Figure 4). For patients with genotypes 2 or 3, however, the SVR rates were uniformly excellent (73% to 78%) regardless of therapy duration or ribavirin dose.^{16,17} Among patients with the most treatment-resistant characteristics (genotype 1 and HCV RNA > 2 million copies/mL), the SVR rate with peginterferon and the higher dose of ribavirin was 46%,¹⁶ similar to that seen in the previous study¹³ (Figure 3).

These findings indicate that patients with treatment-resistant characteristics, such as HCV genotype 1, require prolonged therapy with higher doses

Early virologic response strongly predicts sustained virologic response

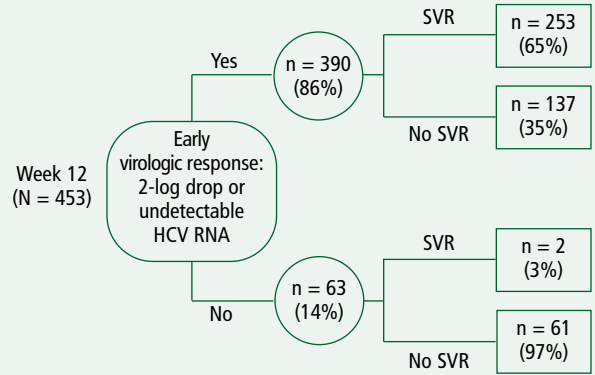


FIGURE 5. Schematic showing rates of sustained virologic response (SVR) in a phase 3 study of peginterferon alfa-2a plus ribavirin according to whether or not patients achieved early virologic response at treatment week 12. Reprinted from ref. 13 with permission. Copyright ©2002 Massachusetts Medical Society. All rights reserved.

of ribavirin to maximize their chance of achieving SVR. At the same time, patients with characteristics favorable to treatment response, such as HCV genotype 2 or 3, can achieve high rates of SVR with less aggressive regimens—namely, only 24 weeks of therapy with peginterferon alfa-2a and ribavirin and/or use of lower doses of ribavirin.¹⁷ Of course, a regimen that reduces the duration of therapy and uses lower doses of ribavirin can decrease both the adverse events and the costs associated with antiviral therapy in patients with genotype 2 or 3.

■ DYNAMIC PREDICTORS OF TREATMENT RESPONSE

Although HCV genotype is the strongest pretreatment predictor of SVR, other factors—such as age less than 40 years, body weight less than 75 kg, and absence of cirrhosis—also have been associated with a favorable response to therapy,^{11,13} although to much lesser degrees. It must be stressed that these pretreatment characteristics give *general* clues to the likelihood of response for a *population* of patients but provide little insight for the individual patient undergoing therapy. While knowledge of these variables is important for counseling patients prior to therapy, a factor that can predict response during treatment has more practical applications.

Prognostic role of early virologic response

Retrospective analyses of the large phase 3 trials of peginterferon alfa-2a and -2b plus ribavirin have

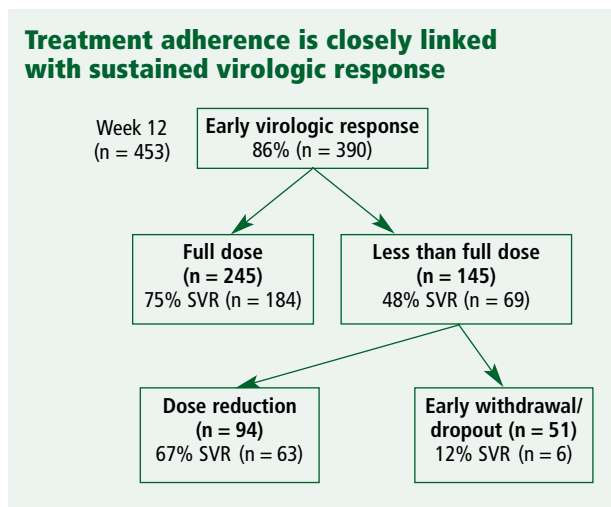


FIGURE 6. Schematic showing rates of sustained virologic response (SVR) in a phase 3 study^{13,20} of peginterferon alfa-2a plus ribavirin according to adherence to the study's medication regimen. "Full dose" was defined as 80% or more of prescribed medication.

assessed the dynamic changes in virologic response during treatment.^{13,18} In the study of peginterferon alfa-2a and ribavirin,¹³ early virologic response (EVR), defined as undetectability of HCV RNA or at least a 2-log (100-fold) decrease in HCV RNA by week 12 of therapy, was shown to be useful in predicting the likelihood of subsequent SVR. As shown in **Figure 5**, 86% of patients treated with peginterferon alfa-2a and ribavirin had EVR. Of these patients, 65% subsequently achieved SVR. Perhaps more important, among the 14% of patients who did not attain EVR, virtually none (3%) subsequently achieved SVR (**Figure 5**).

The clinician can use this information in several ways. Patients achieving EVR can be encouraged to keep adhering to their medication regimens since their chances of ultimately achieving SVR are now increased above baseline. In contrast, if EVR is not achieved, the likelihood of subsequent SVR is so low that the clinician and patient can decide to discontinue treatment prematurely so as to not subject the patient to the continued adverse events and costs of therapy that will have no defined long-term benefits.

Several caveats are necessary, however. Because quantitative viral assays have inherent variability, significant antiviral effect can occur that is somewhat less than the 100-fold reduction cited above.¹⁹ In these situations, treatment should be continued and HCV RNA measured again at 24 weeks to determine if viral eradication has occurred, at which point decisions about therapy continuation can be reevaluated. Additionally, the EVR analysis is also

influenced by HCV genotype. Because virtually all patients with genotype 2 or 3 achieve EVR (97%),²⁰ measurement of HCV RNA at week 12 in these patients probably does not influence management decisions in this group, whose standard course of therapy is only 24 weeks.

■ ADHERENCE IS KEY TO TREATMENT RESPONSE

Adherence to therapy is increasingly recognized as a key determinant in the outcome of antiviral therapy for chronic hepatitis C.^{20,21} Patients who demonstrate EVR and are then able to maintain near-complete adherence to their regimen (> 80% of prescribed medications) have the highest likelihood of achieving SVR (75%) (**Figure 6**). In contrast, patients with lesser degrees of adherence have decreased rates of SVR (48%). Further analysis of the nonadherent group shows that dose modification has a relatively minor effect on the SVR rate (67%), whereas premature discontinuation almost assures treatment failure (12% SVR) (**Figure 6**).^{13,20}

For these reasons, maintaining adherence to therapy must be a major goal for clinicians managing patients with chronic hepatitis C and the importance of adherence must be emphasized to all patients undergoing treatment.

■ SIDE EFFECTS AS BARRIERS TO ADHERENCE

The greatest barriers to adherence are medication side effects, which occur to some extent in all patients undergoing therapy for hepatitis C. These adverse events have a tremendous impact on patients' quality of life and contribute substantially to dose reductions or premature withdrawal during treatment.

In clinical trials, dose reductions (either temporary or permanent) for any adverse event were required in 32% to 42% of patients receiving peginterferon alfa-2a or -2b compared with 27% to 34% of patients receiving standard interferon.^{4,13,22} Rates of premature therapy discontinuation due to adverse events were generally low with both peginterferon alfa-2a plus ribavirin (10%)¹³ and peginterferon alfa-2b plus ribavirin (14%)¹¹ and were comparable to the rates with standard interferon plus ribavirin (11% and 13% in the respective studies).^{11,13}

The side effects of peginterferons vary by preparation. Decreased rates of influenza-like symptoms and depression were noted in patients treated with peginterferon alfa-2a and ribavirin compared with those receiving standard interferon and ribavirin.¹³

These and other less common adverse events associated with peginterferon therapy have been reviewed previously.²²

■ HOW TO MANAGE ADVERSE EVENTS

The management of side effects of medications for hepatitis C should begin even before the first dose is given. Treatment for hepatitis C never constitutes an emergency, so the timing of therapy initiation should be discussed before embarking on the treatment course. Knowledge about impending vacations, important business plans, or other upcoming momentous occasions can help determine when to start therapy in order to minimize the impact of side effects on quality of life and to encourage adherence. Patients should receive detailed instruction in the use of peginterferon and ribavirin and be given comprehensive information about what to expect during therapy.

Simple interventions can yield important improvements in patients' quality of life. Examples include administering peginterferon on Friday evenings in anticipation of less stress on weekends, maintaining adequate hydration, continuing a light to moderate exercise program, and judicious use of acetaminophen or nonsteroidal anti-inflammatory drugs to diminish the influenza-like symptoms and asthenia associated with therapy. Most important, patients receiving therapy must be seen by a health care professional in a supportive environment at regular, frequent intervals to allow for monitoring of adverse events, assessment of their severity, and quick intervention to prevent dose reduction or therapy disruption.

Managing specific adverse events

The most frequent reasons for peginterferon dose reduction are neutropenia and depressive symptoms; the most common cause of ribavirin dose reduction is anemia.⁴ Specific interventions for these adverse events may be useful in many patients.

Neutropenia. In clinical trials, the frequency of dose reduction for neutropenia was greater with both peginterferon agents compared with standard interferon (20% with peginterferon alfa-2a vs 5% with interferon,¹³ and 18% with peginterferon alfa-2b vs 10% with interferon¹¹). Approximately 4% to 5% of peginterferon recipients experienced grade 4 neutropenia (< 500 cells/mm³) in both studies. Neutropenia was not associated with an increased risk of infection.

Dose reduction, suggested for patients with neutrophil counts that fall below 750 cells/mm³, results

Interferon-induced depression: Symptoms should guide antidepressant selection

Depression and the spectrum of related symptoms

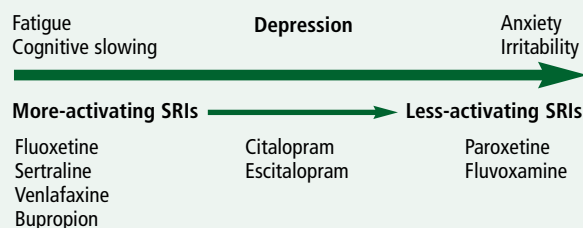


FIGURE 7. Selection of a serotonin reuptake inhibitor (SRI) for interferon-induced depression depends on the individual patient's symptoms. Patients with symptoms such as fatigue and cognitive slowing are candidates for one of the more-activating SRIs, whereas patients with symptoms indicative of higher degrees of activation, such as anxiety or irritability, are candidates for a less-activating SRI.

in a rapid increase of neutrophils within 1 to 2 weeks. Studies are under way to evaluate the safety of lowering the threshold for dose reduction to 500 cells/mm³. In cases of extreme neutropenia or when infection does occur, the use of granulocyte colony-stimulating factor raises neutrophil counts quickly.^{4,22,23}

Anemia. Ribavirin universally induces an extravascular hemolysis due to depletion of erythrocyte ATP stores, leading to increased susceptibility to oxidative damage.²⁴ The average reduction in hemoglobin is approximately 2.5 to 3.0 g, although more significant decreases in hemoglobin and in symptoms associated with anemia are not uncommon, and they can substantially affect quality of life. Dose reduction, recommended for hemoglobin levels that fall below 10 g/dL in patients without any evidence of coronary artery disease, results in a rapid increase in hemoglobin levels.

An emphasis on adherence and maintaining ribavirin dosing has led to a search for alternate strategies to dose reduction. Epoetin alfa (40,000 units/week) was recently shown to maintain ribavirin dosing and to improve quality of life in patients who develop ribavirin-induced anemia.²⁵ Several questions remain, however, including the effects of epoetin alfa on SVR, its cost-effectiveness, and which subgroups of patients may benefit most from its use. At present, we reserve epoetin alfa for patients with markedly symptomatic anemia who require significant reductions in their ribavirin dose to maintain hemoglobin above 10 g/dL or in whom ribavirin discontinuation is immi-

ment because of severe anemia (between 8.5 and 10 g/dL). Initial management of these patients with severe anemia still requires transient ribavirin dose reduction and close monitoring until the hemoglobin values increase after administration of epoetin alfa (generally within 1 to 2 weeks).²²

Depression. Approximately 20% to 30% of patients treated with peginterferon and ribavirin report depression during therapy.^{4,11,13} This makes depression a frequent cause of decreased quality of life and an indication for dose reduction and discontinuation.²² Specific questioning of the patient and his or her family or significant other about depressive symptoms should be undertaken at each follow-up visit during treatment.

Severe depression accompanied by suicidal ideation requires immediate discontinuation of antiviral therapy and immediate referral to mental health professionals. Lesser degrees of depression or other neuropsychiatric side effects can initially be managed with various antidepressant drugs, often in consultation with a local mental health care provider. There is growing consensus that serotonin reuptake inhibitors may be the drugs of choice for treating depression associated with interferon or peginterferon therapy in patients with chronic hepatitis C.²² Because serotonin reuptake inhibitors may be more or less activating (stimulating), the choice of agent should be based on the patient's predominant symptoms²⁶ (Figure 7).

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Treatment options for nonresponders and relapsers to initial therapy for hepatitis C

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■ ABSTRACT

As treatment for chronic hepatitis C virus (HCV) infection has advanced over the past decade, efforts have evolved to retreat patients who did not achieve a sustained virologic response to previous antiviral regimens. Retreating nonresponders to interferon alfa monotherapy with a combination of interferon and ribavirin yields a sustained virologic response in 9% to 32% of patients, whereas retreatment with peginterferon alfa plus ribavirin yields a sustained virologic response in up to 30% to 40% of patients. Sustained virologic response is more likely in retreated patients with HCV genotype 2 or 3, low serum HCV RNA levels, and lack of response to prior interferon monotherapy. Retreatment of nonresponders to interferon-ribavirin combination therapy is associated with lower response rates ($\leq 20\%$). Despite treatment advances, the efficacy of current antiviral regimens for nonresponders remains inadequate. The next few years will see more-targeted antiviral regimens for these patients and therapies focused on slowing the progression of liver disease rather than viral eradication.

Over the past decade, treatments for chronic hepatitis C have evolved from monotherapy with interferon alfa to combinations of pegylated interferon alfa (peginterferon) and ribavirin. As these regimens have evolved, their associated rates of sustained eradica-

tion of hepatitis C virus (HCV) have progressed from levels as low as 5% for a 6-month course of interferon monotherapy to 55% with recent regimens of peginterferon plus ribavirin.¹⁻³

Despite these gains, many patients remain unresponsive to interferon-based therapy or relapse after therapy ends. Retreatment of these patients, especially those in advanced stages of liver disease, remains an important challenge to investigators and clinicians. This article reviews the specifics of this challenge, the progress that has been made to date, and potential regimens and strategies to combat it in the future.

■ CATEGORIES OF RESPONSE TO THERAPY

Any discussion of treatment options for nonresponders to therapy for hepatitis C should begin by defining terms. The 1997 National Institutes of Health Consensus Development Conference clarified the definitions of response patterns to antiviral treatment.⁴ It should be emphasized that as treatment for hepatitis C has evolved, so has the sensitivity of assays for viral load (HCV RNA). Current studies use an HCV RNA threshold of 100 copies/mL or 50 IU/mL as the lower limit of viral detection.

End-of-treatment virologic response is defined as an undetectable level of HCV RNA by polymerase chain reaction at the completion of therapy.^{3,4} With sensitive polymerase chain reaction assays, **sustained virologic response** is defined as an undetectable HCV RNA level 6 months after therapy is discontinued.

In contrast, **nonresponders** are a heterogeneous group of patients who remain positive for HCV RNA during the course of treatment.^{3,4} They may be **true nonresponders**, whose HCV RNA levels are unaffected by treatment, or **partial responders**, who show a significant drop in HCV RNA with treatment but in whom HCV RNA never becomes undetectable.³⁻⁷

Still other patients achieve HCV RNA levels that are undetectable by sensitive assays during therapy but later become detectable as treatment con-

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TABLE 1

Characteristics commonly seen in nonresponders to antiviral therapy for hepatitis C

HCV genotype 1	Male sex
Advanced liver disease (cirrhosis)	African-American race
Serum HCV RNA greater than 2 million copies/mL	Obesity

tinues.³⁻⁸ This **breakthrough** response pattern has an uncertain etiology, but it may result from mutations that render the virus interferon-resistant and contribute to the complexity of HCV quasispecies. This type of response may also result from production of antibodies against interferon.⁵⁻⁷

Finally, **relapsers** are patients in whom HCV RNA is undetectable at the end of a full course of therapy but whose viral levels again become detectable when treatment is discontinued. Such relapses have become less frequent with the advent of regimens that use peginterferon and ribavirin for an adequate length of time.³⁻⁸

Table 1 lists patient characteristics that are frequently associated with inadequate response to antiviral therapy for hepatitis C.

■ INITIAL ANTIVIRAL THERAPY: WHERE WE STAND TODAY

In 2003, standard therapy for previously untreated patients with chronic hepatitis C consists of a combination of peginterferon and ribavirin. Patients with HCV genotype 1 usually require a full 48-week course of this regimen, whereas those with HCV genotype 2 or 3 may require only 24 weeks of therapy.³

Accurate identification of patients unlikely to achieve sustained virologic response relies on a measure known as *early virologic response*, defined as a 2-log drop in HCV RNA after 12 weeks of therapy, or undetectability of HCV RNA after 24 weeks of therapy. Patients who do not achieve an early virologic response are unlikely to respond to a full course of therapy, so this measure can be used to guide decisions to shorten the therapy course for these patients, minimizing potential side effects and costs.

In addition to early virologic response, good adherence to treatment is also associated with sustained virologic response. This is especially true dur-

ing the first 12 weeks of therapy, which is the most critical period.

■ ANTIVIRAL TREATMENT OF NONRESPONDERS: OBJECTIVES AND GENERAL OUTCOMES

The primary goal of antiviral therapy has always been to achieve viral eradication. But as treatment of HCV infection has evolved, additional outcomes have gained importance, such as histologic response (improvement of inflammation and fibrosis on liver biopsy) and health-related quality of life. Histologic response is especially important in nonresponders whose disease has already demonstrated resistance to therapy.⁸ The main goals of therapy in these patients are to reduce hepatic inflammation, slow progression of fibrosis to cirrhosis, and reduce the risk of hepatic decompensation and hepatocellular carcinoma.⁸

The characteristics of patients considered nonresponders have evolved along with the evolution of treatment regimens. At first, most nonresponders had been treated with standard interferon monotherapy, which eradicated HCV in only 15% to 20% of infected patients, leaving 80% to 85% of patients as nonresponders. As more effective treatment with interferon alfa-2b and ribavirin became widely available, the proportion of nonresponding patients dropped to 50% to 60% of the treated group. The advent of combination therapy with peginterferon and ribavirin has reduced the proportion of nonresponding patients further, but it has left us with a nonresponder population that is potentially more difficult to retreat.

Patients previously treated only with interferon monotherapy stand a good chance of viral eradication with a combination of peginterferon and ribavirin. However, viral eradication through retreatment is more difficult in patients who have not responded to combination therapy with interferon and ribavirin. In general, the decision to retreat a nonresponder should be based on the patient's previous pattern of response, the regimen used, the severity of underlying liver disease, the HCV genotype, and the patient's prior drug tolerance (**Table 2**).³

■ REGIMENS FOR NONRESPONDERS

Results with interferon-based regimens

Retreatment with interferon-based regimens has generally been studied in nonresponders to interferon monotherapy.⁸ One study used a 12-month course of consensus interferon for retreatment of nonresponders and reported sustained virologic

response in 27% of patients who had had breakthroughs during their initial therapy but in only 8% of those who had not had breakthroughs during initial therapy.⁹ This suggests that patients with a history of breakthrough are more likely to achieve sustained virologic response with a second course of therapy than are established nonresponders.

Rates of sustained virologic response in retreatment studies using a combination of interferon and ribavirin have ranged from 9% to 32%.¹⁰⁻¹³ Some of these studies used weight-based ribavirin dosing (600 to 1,200 mg/day) and varying doses of interferon alfa-2b (3 to 5 MU three times weekly).^{12,13} Others have tried induction therapy with daily dosing of interferon, achieving sustained virologic response rates of up to 32%.^{10,11} A controlled trial of high-dose induction interferon therapy plus ribavirin versus standard-dose interferon plus ribavirin showed no significant difference in sustained virologic response rates between the two regimens.¹¹

Some of these studies were captured in a meta-analysis that included 789 patients from nine clinical trials; all patients had not responded to initial interferon therapy and underwent 6 months of retreatment with interferon and ribavirin.¹⁴ The analysis revealed a sustained virologic response rate of 13.2% and showed that 14 nonresponders to interferon needed to be treated with interferon-ribavirin combination therapy to achieve 1 additional sustained virologic response.

Just as with interferon-naïve patients, HCV genotype remains an important predictor of response in the retreatment of nonresponders.¹⁴⁻¹⁶ The above meta-analysis¹⁴ could not provide information about the potential benefits of longer retreatment therapy (>6 months) in patients with HCV genotype 1.

Results with peginterferon-based regimens

Data currently are limited on outcomes among nonresponders who are retreated with a combination of peginterferon and ribavirin. Preliminary data are available from an ongoing study of 212 nonresponders to interferon monotherapy or interferon-ribavirin combination therapy.¹⁷ Patients were retreated with peginterferon alfa-2a (180 µg/week) plus ribavirin (1,000 to 1,200 mg/day). Those with detectable HCV RNA at week 20 were defined as nonresponders and switched to maintenance therapy with peginterferon alfa-2a, while those without detectable HCV RNA continued a full course of combination therapy for 48 weeks.

An end-of-treatment response was reported in 53% of patients, but a sustained virologic response in

TABLE 2
Factors to consider before retreatment
a nonresponding HCV-infected patient

Severity of liver disease	Tolerance of prior therapy
HCV genotype	Prior regimen used
Prior pattern of response to therapy	

only 20%.¹⁷ The rate of sustained virologic response was higher in patients previously treated with interferon monotherapy (34%) than in those previously treated with interferon plus ribavirin (11%). Rates of sustained virologic response also were higher in patients with HCV genotypes other than genotype 1 (60% vs 15%), patients younger than age 50 (25% vs 13%), non-African Americans (22% vs 0%), and patients with at least a 2-log decline in HCV RNA from baseline to treatment week 12 (41% vs 7%).¹⁷

Similar findings emerged from a retreatment study of 17 nonresponders to prior interferon monotherapy and 84 nonresponders to prior interferon-ribavirin combination therapy.¹⁸ Patients received 1 µg/kg/week of peginterferon alfa-2b plus 1,000 to 1,200 mg/day of ribavirin or 1.5 µg/kg/week of peginterferon alfa-2b plus 800 mg/day of ribavirin. Rates of sustained virologic response were 40% in the first group and 25% in the second group. Among patients who had received prior interferon-ribavirin combination therapy, the sustained virologic response rate was less than 11%.¹⁸

In a similar study,¹⁹ patients who had relapsed after interferon-ribavirin combination therapy showed end-of-treatment response rates of 71% to 76% after 24 weeks of retreatment with peginterferon plus ribavirin. In comparison, end-of-treatment response rates ranged from 26% to 52% in nonresponders to prior interferon monotherapy or interferon-ribavirin combination therapy.

Preliminary results from a trial of triple therapy with amantadine plus peginterferon alfa-2b and ribavirin suggest a sustained virologic response rate of 19.4% among nonresponders to prior interferon-ribavirin combination therapy.²⁰

■ ALTERNATIVE THERAPIES FOR VIRAL SUPPRESSION

Amantadine, an antiviral agent with activity against influenza A, is a less well-defined treatment option for chronic hepatitis C. Despite early enthusiasm,

amantadine monotherapy has shown little efficacy in patients with HCV infection. Furthermore, adding amantadine to standard interferon seems to confer little additional efficacy against HCV. In two trials in nonresponders to interferon monotherapy, retreatment with interferon plus amantadine yielded a 0% sustained virologic response rate.^{21,22}

Amantadine has also been studied as part of a triple-therapy regimen in combination with interferon and ribavirin. This triple regimen has met with mixed results, producing sustained virologic response in 48% of nonresponders to interferon in one study²³ but in less than 20% of nonresponders to interferon and/or to interferon-ribavirin combination therapy in two other studies.^{20,24}

■ STRATEGIES FOR IMPROVING HISTOLOGY IN VIROLOGIC NONRESPONDERS

Maintenance therapy for hepatitis C is based on the premise that long-term interferon therapy may yield histologic improvement. Despite the lack of a virologic response, histologic improvement has been reported in about 40% of nonresponders to interferon-based therapy.²⁵ Though it does not eradicate the virus, continued interferon therapy may prevent histologic progression to cirrhosis. In one study, nonresponders to interferon monotherapy were randomized to observation or to interferon alfa-2b (3 MU three times weekly) for 2.5 years.²⁶ Patients receiving therapy showed further declines in HCV RNA titer and some reduction in fibrosis, whereas HCV titers returned to baseline and fibrosis progressed in the observation group.

Several trials are addressing the potential efficacy of maintenance regimens. Patients in the ongoing Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial¹⁷ who remained positive for HCV RNA after 20 weeks of combination therapy with peginterferon alfa-2a and ribavirin were randomized to a weekly maintenance dose of peginterferon alfa-2a alone. The results of this study are expected to show whether long-term maintenance therapy with peginterferon can prevent hepatic fibrosis from progressing and delay complications of advanced liver disease.

Other agents that may help prevent progression of hepatic fibrosis include ursodeoxycholic acid, colchicine, and interferon gamma.

Several clinical trials have shown that ursodeoxycholic acid is associated with a decline in serum alanine aminotransferase levels in HCV-infected patients without a significant impact on serum HCV

RNA or improvement of hepatic histology.²⁷⁻²⁹

Colchicine has been used to treat chronic hepatitis C because of its potential antifibrotic effect. However, one trial showed a lower end-of-treatment virologic response rate with the combination of colchicine plus interferon (23%) than with interferon alone (47%), suggesting a lack of antiviral effect for colchicine.³⁰ Nevertheless, a long-term trial (the Co-Pilot study) randomizing nonresponding patients to a maintenance dose of peginterferon alfa-2b or colchicine is under way.

Interferon gamma seems to have a predominant antifibrotic activity and is being tested in a large multicenter study of patients with HCV infection and advanced fibrosis.

■ SCREENING FOR AND PREVENTING HEPATOCELLULAR CARCINOMA

The incidence of hepatocellular carcinoma (HCC) in the United States is rising, having climbed from 1.4 per 100,000 population in 1991 to 2.4 per 100,000 population in 1995.³¹ This increase continued throughout the 1990s and is attributed mainly to HCV infection.³¹ The morbidity, mortality, and economic burden of HCV infection are expected to be substantial over the next decade.^{31,32}

Rationale for HCC screening

HCC has a variable natural history. Because tumor size can increase rapidly (median doubling time ranges from 4 to 6 months), screening for HCC with serum alpha fetoprotein monitoring and hepatic ultrasonography has been recommended in HCV-infected patients.³² Early detection of HCC may lead to improved 5-year survival rates: 60.5% with tumors smaller than 2 cm in diameter, 39.3% with tumors 2 to 5 cm, and 26.8% with tumors larger than 5 cm.³³

A recent prospective study³⁴ of 163 HCV-infected patients who were followed for 5 to 7 years with serial ultrasonography and alpha fetoprotein monitoring suggested that the risk for HCC was associated with male sex, age greater than 60, and HCV genotype 1b. Patients with cirrhosis were at the highest risk for HCC, with an annual incidence of 2.5%. While advanced age, male gender, and underlying cirrhosis are known risk factors for HCC, specific HCV genotypes have not been consistently associated with this malignancy. Of the 163 HCV-infected patients in this study, 22 developed HCC over the follow-up period. The tumor was monofocal in 72% of these patients, with a mean diameter of 20.5 mm. Many of the tumors

were amenable to resection, transplantation, or other ablative therapy, including percutaneous ethanol injection and transarterial chemoembolization.

Another study³⁵ compared the feasibility of surgery between patients infected with HCV or hepatitis B virus who were screened to identify early, subclinical HCC and patients who presented with symptomatic HCC. Significantly more of the screened patients were able to undergo surgery or chemoembolization than were their nonscreened counterparts, and this translated to significantly improved cumulative survival for the screened patients. Although these data require confirmation, this study supports the value of screening programs for HCC in HCV-infected patients.

Antiviral treatment may help prevent HCC

The impact of antiviral therapy on HCC is another important area of research. Interferon therapy has been associated with reduced incidence rates of HCC in HCV-infected patients.

In a retrospective analysis of 2,890 patients with chronic hepatitis C, HCC developed in 3.7% of those who had been treated with interferon compared with 12% of those who had gone untreated.³⁶ This study also confirmed that patients with advanced fibrosis were at an increased risk of developing HCC. Other retrospective studies have supported this study's findings, showing that 6.7% to 7.6% of interferon-treated patients with chronic hepatitis C developed HCC compared with 12.4% to 13.2% of untreated patients.^{37,38}

A recent prospective study of 90 patients with chronic hepatitis C confirmed these results and reported a risk ratio of 0.256 (95% CI, 0.125 to 0.522) for HCC with interferon therapy compared with symptomatic treatment over 8.7 years of follow-up.³⁹ HCC was diagnosed in 73% of the control patients vs 27% of the interferon-treated patients.

Another prospective study⁴⁰ followed patients with hepatitis C for 8 to 11 years after completion of interferon therapy and again found low annual incidence rates of HCC: 0.37% in patients who were complete responders and 0.5% in those who were biochemical responders (ie, patients with sustained normal alanine aminotransferase levels without viral clearance). This compared with an annual incidence of 1.2% in untreated control patients with hepatitis C.

A small trial suggests that postoperative interferon therapy may prevent recurrence of HCC after resection.⁴¹ This study randomized 30 patients with HCV-related HCC to postoperative interferon therapy for 104 weeks or to no therapy. Over a 2-year period fol-

lowing resection, HCC recurred in 12 of 15 patients in the control group compared with 5 of 15 in the treated group. Notably, recurrence of HCC, either from metastases or from new foci (multicentric occurrences), was also less frequent in patients without detectable virus than in those with ongoing viremia.

In addition to these encouraging results with standard interferon, peginterferons are being studied for use as maintenance therapy. Notably, HCC is an important long-term outcome that is being assessed in the ongoing HALT-C trial,¹⁷ discussed above, which is using peginterferon alfa-2a for maintenance therapy.

SUMMARY AND RECOMMENDATIONS

Recommendations for retreatment of nonresponding or relapsing patients with hepatitis C have been frequently revised with the introduction of new therapies over the past decade. Currently, patients who have not responded to interferon monotherapy or interferon-based combination therapy may benefit from a course of peginterferon and ribavirin. However, rates of sustained virologic response in nonresponders to combination therapy with standard interferon and ribavirin generally remain low. The decision to retreat should be based on the patient's stage of liver disease, HCV genotype, and tolerance of previous regimens.

Even after trying all available treatment options, many patients with chronic hepatitis C remain nonresponders. Alternative regimens with antifibrotic agents and maintenance regimens are being considered for these patients, especially for those with significant hepatic fibrosis. Maintenance therapy with peginterferon alone or with alternative therapies may ultimately be shown to prevent progression to cirrhosis and HCC. For now, patients at high risk for HCC should be considered for clinical trials designed to address this issue. These patients also should be considered for screening programs to identify HCC at an early and more treatable stage.

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Special management challenges in hepatitis C

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■ ABSTRACT

Infection with hepatitis C virus (HCV) often coexists with other conditions and patient factors that complicate its management. Infection with HIV is a particularly widespread and vexing comorbidity of HCV infection, since HIV facilitates HCV transmission and renders HCV more opportunistic. This review provides a practical overview of major comorbidities and patient factors that require special management considerations in patients with HCV infection.

In and of itself, infection with hepatitis C virus (HCV) poses a challenge to the clinician, both for the scope of the pathology it can cause and for the management it requires. Yet its management is more daunting when we consider that HCV infection often coexists with other comorbidities, adding further complexity to clinical decision-making. This article reviews considerations surrounding coinfection with human immunodeficiency virus (HIV) and other major factors that demand special attention when managing patients with HCV infection.

I. Coinfection with HIV

Coinfection with HIV and HCV has become widespread: approximately 25% to 30% of all HIV-positive patients in the United States, or about 200,000 to 300,000 persons, are also infected with HCV.¹ The frequency of coinfection varies among subgroups of patients: it is as low as 4% to 10% in HIV-positive men who have sex with men, as high as 50% to 90% in HIV-positive injection-drug users, and 98% in HIV-positive hemophiliacs.²⁻⁴

These figures, although high, may underestimate the true frequency of coinfection, since 4% of coinfecting patients have been reported to have a negative

HCV antibody test despite documented HCV viremia.⁵ Therefore, when HCV coinfection is highly suspected, a negative antibody test should not rule out infection and should be complemented with HCV RNA testing by polymerase chain reaction (PCR).⁶

■ HIV ENHANCES HCV TRANSMISSION

HIV appears to facilitate both the sexual and the vertical (mother-to-infant) transmission of HCV.

Among sexually active homosexual men, HCV infection is three times as frequent in those who are HIV-positive as in those who are HIV-negative.^{7,8} Similarly, several studies show a consistently higher rate of vertical transmission of HCV among mothers infected with both HIV and HCV as compared with mothers infected with HCV only.⁹⁻¹² In one study, HIV coinfection in the mother imparted an odds ratio of 3.76 (95% confidence interval [CI], 1.89 to 7.41) for transmission of HCV to the infant.¹¹ In another study, the rate of vertical HCV transmission was 18.2% among mothers infected with both HIV and HCV compared with 6.4% among those infected with HCV alone.¹² Many other variables can modulate this risk of vertical transmission in individual patients, including HCV viral load and the mode of delivery.¹¹

■ HOW THE VIRUSES AFFECT EACH OTHER

Before the era of highly active antiretroviral therapy (HAART) for HIV infection, AIDS-related conditions accounted for most deaths in HIV-infected patients. In contrast, end-stage liver disease is now emerging as a major cause of morbidity and mortality in this population. A recent report from one major US medical center indicated that end-stage liver disease was the cause of death in 50% of the center's HIV-positive patients in 1999, up from just 11.5% in 1991; 90% of these HIV-positive patients who died from liver disease in 1999 were positive for HCV.¹³

HIV makes HCV opportunistic

In the setting of HIV infection, HCV behaves more aggressively, with higher rates of replication and high-

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er degrees of liver damage. This manifests as follows:

Lower rates of infection clearance. Spontaneous clearance of HCV occurs in up to 15% to 30% of patients who are not coinfecting with HIV,¹⁴ compared with only 5% to 10% of those who are coinfecting.¹⁵

Higher rates of viral replication. Patients with HIV coinfection seem to have higher HCV RNA levels than their counterparts without HIV.¹⁶ In one study of HCV-infected injection-drug users,¹⁷ those who were also infected with HIV had a significantly higher HCV viral load than those who were not (7.19 log vs 6.73 log; $P < .001$).

More frequent progression to cirrhosis. Several studies suggest that patients with HIV–HCV coinfection progress to cirrhosis significantly sooner than those with HCV infection alone, even after adjusting for alcohol consumption. In a study from Spain,¹⁸ the mean estimated interval from HCV infection to cirrhosis was 7 years in patients coinfecting with HIV vs 23 years in those infected with HCV alone. Also, the degree of CD4⁺ cell deficiency has been linked with an increased risk of progression to liver fibrosis: patients with CD4⁺ cell counts less than 500 cells/mL were 3.2 times more likely (95% CI, 1.1 to 9.2) to have advanced fibrosis on liver biopsy than were patients with a better-conserved immune system.¹⁹

Earlier development of hepatocellular carcinoma. A recent report from Spain²⁰ found that hepatocellular carcinoma occurred at a younger age (mean 42 years vs 69 years) and after a shorter interval of HCV infection (mean 18 years vs 28 years) in HIV-coinfecting patients than in those without HIV.

HCV's effect on HIV is more equivocal

Whether HCV behaves as a cofactor for HIV progression is controversial. In the Swiss HIV Cohort Study,²¹ which included 1,157 patients coinfecting with HIV and HCV, the presence of HCV was independently associated with progression to an AIDS-defining condition or death (hazard ratio of 1.7 [95% CI, 1.26 to 2.30]). HCV also was associated with less robust CD4⁺ cell recovery after HAART, but it did not predict HIV virologic response to HAART. Daar et al²² showed that increases in HCV viral load are associated with progression of HIV disease: for every 1-log increase in HCV RNA, there was a 1.66 relative risk (95% CI, 1.1 to 2.51) for progression to AIDS.

In contrast, Sulkowski et al²³ found no difference in the risk of developing AIDS-defining conditions, the risk of death, or the increase in CD4⁺ cell count during HAART between 873 HIV/HCV-coinfecting patients and 1,082 patients with HIV infection alone.

Some have speculated that HIV–HCV coinfection may reflect poorer adherence to medication regimens, since it is often a marker for injection-drug use.⁶

HAART and HCV: Do they mix?

It also is controversial whether HAART changes the progression of HCV-associated liver disease. Some have suggested that there may be an immune reconstitution phenomenon whereby the liver inflammatory pattern could worsen upon the start of HAART and improvement in the patient's cellular immune function. One study reported a transient increase in HCV viral load, in aminotransferase levels, and in mean score on the Knodell histology index (from 8 to 13) after the start of HAART.²⁴ Other studies found HAART to have no impact on HCV replication,^{25,26} and another indicated that HAART had a protective effect on progression of liver fibrosis.²⁷

All antiretroviral drugs have been implicated in some degree of liver toxicity. However, HCV infection is well established as an independent risk factor for the development and increased severity of liver toxicity in patients starting or receiving HAART. Sulkowski et al²⁸ reported a 12% incidence of severe hepatic damage among 211 HIV-infected patients receiving protease inhibitor–based HAART regimens, and HCV infection was a strong predictor of its occurrence. Martinez et al²⁹ reported a 9.7% incidence of severe hepatotoxicity among 610 HIV-infected patients receiving nevirapine-based HAART; 51% of the study population was also infected with HCV, and hepatotoxicity was predicted by the cumulative time on antiretroviral drugs and by HCV infection.

■ MANAGING COINFECTION PATIENTS

Assessing for HCV. Guidelines from the US Public Health Service and the Infectious Diseases Society of America recommend that every HIV-infected person be tested for HCV infection by enzyme immunoassay. However, up to 4% of patients who are truly coinfecting with HIV and HCV may have a false-negative result for HCV by enzyme immunoassay.⁵ Therefore, when risk factors are present, or if there is an unexplained elevation of liver function test values, HCV viral load should be assessed by reverse transcriptase PCR. Once the presence of replicating HCV has been established, further characterization and staging should be strongly considered, following the general principles outlined earlier in this supplement.

When to treat HCV infection. Soriano et al³⁰ found that a CD4⁺ cell count greater than 500

cells/mL in patients with HIV–HCV coinfection is associated with an increased likelihood of HCV virologic response to interferon alfa (“interferon” hereafter). Patients with counts above 350 cells/mL (or > 300 cells/mL with HIV viral load under control) are generally considered eligible for HCV therapy.

Ideally, treatment of hepatitis C in patients with HIV–HCV coinfection would precede the initiation of HAART, since patients would have more conserved immune function, less risk of opportunistic infections, and no added toxicity or interactions between drug regimens. However, most patients with coinfection are already on HAART when HCV infection is discovered. As long as awareness about drug interactions, added side effects, and medication adherence is kept high, concurrent treatment of the two viruses is not contraindicated. Patients with low CD4⁺ cell counts should probably delay HCV treatment until HAART has resulted in a better immune status.³¹

Patients with HIV–HCV coinfection are candidates for HCV therapy if they have any of the following:³¹

- HCV genotype 2 or 3
- HCV genotype 1 and elevated alanine aminotransferase levels
- Normal alanine aminotransferase levels and a biopsy with any degree of fibrosis.

The timing of therapy depends on the clinical factors outlined above.

Treatment success rates. The largest series of patients with HIV–HCV coinfection to date (N = 111) showed a 28% end-of-treatment HCV response rate with the combination of interferon and oral ribavirin.³² Overall estimates of the end-of-treatment and sustained virologic response rates for this combination in patients with HIV–HCV coinfection are 35% and 25%, respectively.³¹

As detailed earlier in this supplement, the combination of peginterferon alfa (“peginterferon” hereafter) and ribavirin has become the regimen of choice for treating HCV infection. The use of this combination in patients with HIV–HCV coinfection has so far been addressed only in preliminary reports. The French RIBAVIC investigators³³ reported a 44% virologic response rate at the end of 48 weeks of treatment among 110 coinfecting patients receiving peginterferon and ribavirin. Chung et al³⁴ reported a 53% combined virologic and histologic response rate at 24 weeks of therapy among coinfecting patients receiving peginterferon and ribavirin.

To put these numbers in perspective, the overall end-of-treatment and sustained virologic response rates are usually reported to be about 10% higher in

patients infected with HCV alone.

Side effects to watch for. Treatment with interferon is challenging, as patients usually feel fatigued and typically lose weight (10 kg, on average). Patients taking interferon or peginterferon usually have reductions in hemoglobin and white blood cells and in the absolute number (but usually not the percentage) of CD4⁺ cells.³⁵ In a study of 20 patients with HIV–HCV coinfection who were treated with interferon and ribavirin, the mean CD4⁺ cell count fell from 350 to 284 cells/mL at 6 months, with no change in the percentage of CD4⁺ cells.³⁶

Drug interactions. Interactions between ribavirin and several common components of HAART regimens should be a paramount consideration when planning for HCV therapy. Ribavirin inhibits the phosphorylation of pyrimidine analogs (zidovudine, zalcitabine, and stavudine) to the active triphosphate form.³⁷ This effect has not been shown to translate to clinical failure of either ribavirin or the pyrimidine analogs,³⁸ although there is an additive effect of ribavirin and zidovudine on the incidence of anemia.

Ribavirin increases the conversion of didanosine to its active metabolite, and concurrent use of these two drugs may increase the risk of pancreatitis.³⁵ Moreover, ribavirin may inhibit mitochondrial DNA polymerase, and it has been reported to raise the incidence of HAART-related mitochondrial toxicity.³⁹

II. Other challenges and difficult-to-treat groups

Other patient factors and comorbidities confer added risks for HCV infection or complicate patient management. These include immunosuppression (eg, due to solid-organ transplantation, diseases requiring immunosuppressive therapy, or chronic renal failure requiring hemodialysis), various extrahepatic or autoimmune manifestations, and membership in certain high-risk demographic groups. Because many patients with these and other special factors have been excluded from large efficacy trials of hepatitis C therapies,⁴⁰ controlled studies in these patients are needed. In the meantime, management of HCV-infected patients with these factors should be informed by the special considerations reviewed below.

■ PSYCHIATRIC DISORDERS: Risk factor for infection, frequent side effect of therapy

Risk-seeking behaviors among people with a psychiatric diagnosis make this population vulnerable to

increased rates of HIV and HCV infection. Rosenberg et al⁴¹ reported an HCV prevalence of 19.6% among 931 patients with severe mental illness, which is 11-fold higher than that in the general US population.

The presence of a psychiatric or substance-abuse diagnosis in an HCV-infected patient poses a great challenge, since interferon or peginterferon may exacerbate or precipitate mental illness. Depression occurs in 16% to 29% of interferon-treated patients, anxiety or emotional lability in 3% to 34%, and insomnia in 18% to 24%.⁴² Irritability, nervousness, fatigue, and impaired concentration are also common. The most concerning, though rare, reported events include suicide, suicidal or homicidal ideation, and relapse into drug addiction or drug overdose.

Although several reports suggest that patients with psychopathologic symptoms before starting interferon therapy may have more severe adverse psychiatric effects in response to treatment,^{43,44} other groups believe that patients with a psychiatric diagnosis can successfully complete interferon therapy.⁴⁵⁻⁴⁷ Some argue that withholding therapy from members of a stigmatized class "raises questions about fairness and discrimination."⁴⁸ The use of interferon or peginterferon therapy in psychiatric patients should be coupled with heightened awareness, closer follow-up, and more thorough probing for psychological disturbance.

■ RENAL DISEASE: Optimal HCV therapy unclear

HCV has a well-described association with mixed cryoglobulinemia and a variety of renal lesions, of which the most prominent is membranoproliferative glomerulonephritis.⁴⁹ Although severe nephrotic syndrome and rapidly progressive glomerulonephritis often require steroids, cytotoxic agents, or plasmapheresis for their management, milder forms of renal involvement respond to antiviral treatment alone.⁵⁰ The optimal therapeutic algorithm and the role of peginterferon in this setting still need to be established by carefully designed clinical trials.

■ RENAL FAILURE: Dialysis carries high infection risk, restricts treatment options

HCV infection is common in patients undergoing hemodialysis. Antibodies to HCV were found in 9.3% of patients participating in the 1997 National Surveillance of Dialysis Associated Diseases in the United States.⁵¹ Additionally, because of the diffuse immune dysfunction associated with end-stage renal

disease (ESRD), up to 3% of serologic tests for HCV in ESRD patients are reported to be false-negative.⁵² PCR testing for HCV RNA has shown that the prevalence of HCV infection among dialysis patients can be as high as 20% to 30%.⁵¹

Because there is a risk for significant liver disease and because cirrhosis is a contraindication to kidney transplantation, liver biopsy should be performed early in dialysis patients who test positive for HCV RNA, to assess the histologic impact of the liver disease.⁵³ Combined liver-kidney transplantation may be considered in selected dialysis patients with cirrhosis.⁵³

The mainstay of HCV therapy for ESRD patients has been interferon. It is usually given at a dosage of 3 MU subcutaneously three times a week after each hemodialysis session, for 6 to 12 months. Sustained virologic response rates have ranged from 15% to 64% in dialysis patients treated before kidney transplantation and followed for up to 19 months.^{54,55} Reduced clearance of interferon in ESRD patients seems to account for the increased side effects and reduced tolerability in these patients, but it also accounts for greater efficacy than would be expected with interferon monotherapy in other patients. Peginterferon's role in patients with ESRD needs to be established in controlled trials.

Use of ribavirin in patients with chronic renal failure is associated with accumulation in erythrocytes and a profound and lasting hemolytic anemia. Although ribavirin's package insert lists creatinine clearance lower than 50 mL/min as a contraindication to its use, Bruchfeld et al⁵⁶ reported a pilot study of interferon-ribavirin combination therapy in 6 HCV-infected patients undergoing dialysis. Reduced ribavirin doses were used (mean of 170 to 300 mg/day), plasma levels were monitored, and patients were closely followed for development of anemia. Four of the 6 patients had end-of-treatment response, but only 1 had sustained virologic response at 10 months.

■ KIDNEY TRANSPLANT: Little role for interferon

Liver failure from chronic hepatitis C is a leading cause of death among long-term survivors of kidney transplantation.⁵⁷ Studies that have used interferon for treatment of HCV infection in renal transplant recipients have included small numbers of patients and have shown low rates of SVR (~ 10%).⁵⁸ Moreover, the use of interferon in this setting has raised concern over the precipitation of acute rejection, acute renal failure, and graft dysfunction (reported at incidences of 15.4% to 63.6% in various series⁵²). Therefore, use

of interferon is relatively contraindicated in kidney transplant recipients; if considered, it should be reserved for experts or the setting of clinical trials.

Transplant can be successful in HCV-infected patients. In some series, liver transplant recipients with HCV infection have been able to undergo kidney transplantation with a reasonable degree of success. Kidney transplantation should be offered for ESRD after liver transplantation, even in the presence of HCV infection, to patients with stable liver function and no signs of liver failure.⁵⁹

Studies assessing the impact of kidney transplantation on survival in HCV-positive patients with ESRD have shown that patients who received a kidney transplant had better survival than their counterparts who were awaiting transplantation.⁶⁰

■ LIVER TRANSPLANT: Risk of recurrent HCV remains

Worldwide, HCV infection remains the main indication for orthotopic liver transplantation (OLT). In patients with demonstrable HCV viremia before transplantation, reinfection of the graft occurs almost universally. HCV-induced damage shows an accelerated course thereafter, so that graft cirrhosis develops in 20% to 30% of patients at 5 years.⁶¹

Several factors have been identified as markers for severe HCV recurrence after OLT,⁶² including:

- High pretransplant or early post-transplant levels of HCV
- HCV genotype 1b
- Coinfection with cytomegalovirus
- The number of rejection episodes (probably as a marker of cumulative immunosuppressive load).

Several strategies have been advocated for treating HCV recurrence following OLT: preemptive treatment before transplant, early post-transplant therapy, or targeted therapy once recurrence is established. Studies of interferon and ribavirin have shown end-of-treatment response rates of about 30% and sustained virologic response rates of about 20%.^{63,64} However, increased rates of side effects, primarily severe anemia, have been observed, so that ribavirin dose modification (based on renal function) is recommended.⁶⁵

So far, the use of peginterferon has been reported in the setting of retreatment for HCV-infected OLT recipients who are nonresponders to interferon and ribavirin. Smallwood et al⁶⁶ reported sustained virologic response in 3 of 15 patients (20%) in this setting. Clearly, further studies are needed to assess the value of peginterferon as initial therapy for recur-

rent HCV infection in OLT recipients.

■ PREGNANCY: Ribavirin demands its exclusion

The teratogenic effects of ribavirin are of utmost concern in female patients of childbearing age. HCV-infected women who take regimens that include ribavirin must absolutely assure that they avoid pregnancy during treatment and for 6 months after completing treatment. Treatment of HCV can always be deferred until after pregnancy.

At the same time, mother-to-infant transmission of HCV can be a concern, especially in women with HIV-HCV coinfection. As detailed above, vertical transmission of HCV is increased threefold when an HCV-infected woman is also infected with HIV.¹² Additionally, in one study vertical transmission of HIV occurred more often in mothers who were coinfecting with HCV than in mothers with HIV alone.⁶⁷

■ AFRICAN AMERICANS: More likely to be infected, less responsive to therapy

HCV infection poses special problems in African Americans, whose infection rate (2.5% to 3.5%) is twofold to threefold higher than that of the general US population.⁶⁸ An estimated 22% of HCV-infected Americans are African American.⁶⁹

The prevalence of HCV genotype 1 in African Americans is as high as 95%. In an early study of consensus interferon monotherapy, the sustained virologic response rate in African Americans was 2%, or one sixth the rate of all patients treated.⁷⁰ This lower response rate was confirmed in a reanalysis of five large trials of interferon monotherapy.⁷¹ Adding ribavirin to interferon increases the response rate but has shown a variable effect on sustained virologic response among African Americans. A recent study of combination therapy with interferon and ribavirin among 99 US veterans (42 of them African American) found sustained virologic response in 18% of white patients (and in 26% of those who completed therapy) but in none of the African Americans.⁷²

Response rates to peginterferon and ribavirin among African Americans are difficult to discern from published studies. In one study,⁷³ univariate analysis suggested that white vs nonwhite status predicted response to treatment, but this is not the same comparison as African Americans vs "other." However, multivariate analysis of the same study found that white vs nonwhite status did not predict response. Only 5% of the 1,121 patients in this series were African American.⁷³

The observed lower treatment response rates in African Americans may have multiple causes. Iron in the liver may impede response to antiviral therapy. African Americans with HCV infection are 5.4 times as likely as whites to have increased ferritin or transferritin saturation levels.⁷⁴ Even more important, the viral dynamics of HCV appear markedly different between African Americans and whites. It is well known that viral kinetics in response to interferon follows a two-phase dynamic. Within 24 to 48 hours after initiation of interferon monotherapy there is a very rapid (0.5- to 2.0-log) decline in viral counts. This is followed by a much slower further decline in viral counts over many months. The first-phase decline in viral counts is 0.8 log lower in African Americans than in whites. The second phase also reveals slower viral elimination.⁷⁵ Others have noted that in African Americans the vigorous CD4-proliferative response to HCV infection was not accompanied by the expected increased production of gamma interferon, suggesting a dysfunctional CD4 response to HCV in African Americans.⁷⁶

Treatment recommendations for the HCV-infected African American patient are difficult at this time. Clearly, those who are eligible should be considered for controlled clinical trials. Otherwise, treatment needs to be individualized. We recommend antiviral therapy with pegylated interferon and ribavirin for African Americans with HCV genotype 2 or 3. For those with genotype 1, the decision should be made by the patient, armed with the best data available. More African Americans clearly need to be included in studies of newer therapeutic strategies.

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